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Canadian Environmental Protection Act, 1999

PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

N,N-Dimethylformamide

Canada

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PRIORITY SUBSTANCES LIST ASSESSMENT REPORT

N,N-Dimethylformamide

Environment Canada
Health Canada

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List of Acronyms and Abbreviations

ACN	acrylonitrile
ALT	alanine aminotransferase
AMCC	N-acetyl-S-(N-methylcarbamoyl)cysteine
AP	alkaline phosphatase
AST	aspartate aminotransferase
BMC_{05}	concentration estimated to cause a 5% increase in incidence over background response rate
BMD	benchmark dose
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CFC	chlorofluorocarbon
CHO	Chinese hamster ovary
CI	confidence interval
CTV	Critical Toxicity Value
DMF	N,N-dimethylformamide
EC_{50}	median effective concentration
ECG	electrocardiograph
EEV	Estimated Exposure Value
ENEV	Estimated No-Effects Value
gamma-GT	gamma-glutamyl transpeptidase
GWP	Global Warming Potential
HMMF	N-(hydroxymethyl)-N-methylformamide
IC_{50}	median inhibitory concentration
K_{oc}	organic carbon/water partition coefficient
K_{om}	soil sorption coefficient
K_{ow}	octanol/water partition coefficient
kg-bw	kilogram body weight
LC_{50}	median lethal concentration
LCL_{05}	lower confidence limit of the BMC_{05}
LD_{50}	median lethal dose
LOAEC	Lowest-Observed-Adverse-Effect Concentration
LOAEL	Lowest-Observed-Adverse-Effect Level
LOEC	Lowest-Observed-Effect Concentration
LOEL	Lowest-Observed-Effect Level
NMF	N-methylformamide
NOAEL	No-Observed-Adverse-Effect Level
NOEC	No-Observed-Effect Concentration
NOEL	No-Observed-Effect Level
ODP	Ozone Depletion Potential
POCP	Photochemical Ozone Creation Potential
PSL	Priority Substances List

PVC	polyvinyl chloride
SCE	sister chromatid exchange
SGOT	serum glutamate–oxalate transaminase
SGPT	serum glutamate–pyruvate transaminase
SIR	standardized incidence rate
TC	Tolerable Concentration
TWA	time-weighted average
UDS	unscheduled DNA synthesis
VOC	volatile organic compound

SYNOPSIS

N,N-Dimethylformamide (DMF) is a colourless liquid at room temperature and has a high water solubility and low vapour pressure.

Canadian production capacity is estimated at less than 10 000 tonnes per year. The majority produced in and imported into Canada is subsequently exported, with the total domestic demand in the range of less than 1000 tonnes per year. The oil and gas/petrochemical sector reportedly accounted for 22% of the total reported quantity used in Canada during 1996, primarily for gas stream separation. During the same year, the formulation of pesticides accounted for approximately 66% of the DMF reportedly used in Canada. These uses are regulated under the *Pest Control Products Act*.

DMF appears to enter the Canadian environment primarily from industrial releases to air. In 1996, about 16 tonnes were reportedly released to the environment from various industrial locations in Canada. Of this total, 15 tonnes were released to air and less than 1 tonne was released directly into surface water. The available information suggests that spills of DMF during use, storage or transport are not a significant route of entry to the environment.

Because of the complete solubility of DMF in water, it is expected that some DMF can be transported from air to surface water or soil (pore water) in precipitation. Atmospheric photooxidation is estimated to take place over a period of days. Releases to water or soil are expected to be followed by relatively rapid biodegradation (half-life 18–36 hours). Abiotic degradation processes and sorption to soil are expected to be minimal.

No data on concentrations in ambient air or surface water in Canada were identified, and data on DMF concentrations in Canadian soil and groundwater are very limited. However, as most DMF is reported to be released to air and as little transfer to water and soil is expected, this assessment has focused on the potential effects on terrestrial organisms exposed by contact with contaminated air. The highest levels of DMF in air are assumed to be found in the immediate vicinity of the industrial facility with the greatest reported annual releases. A conservative estimate of concentrations near this point source provides an Estimated Exposure Value that is generally higher than or comparable to measurements recorded in other countries.

Environmental toxicity data are available for a range of terrestrial and aquatic organisms. Based on a comparison of the highest estimated concentration in air with the estimated no-effects concentration derived from experimental data for terrestrial biota, it is unlikely that organisms are exposed to harmful levels of DMF in the Canadian ambient environment.

DMF is not involved in the depletion of stratospheric ozone. Because of its reactivity and the relatively small amounts of DMF released to the atmosphere, it is not expected to play a role in climate change or ground-level ozone formation.

Quantitative data on concentrations of DMF in drinking water, food, indoor air or ambient air in Canada were not identified. Air in the vicinity of point sources appears to be the greatest potential source of exposure of the general population to DMF. Based on the results of epidemiological studies of exposed workers and supporting data from a relatively extensive database of investigations in experimental animals, the liver is the critical target organ for the toxicity of DMF. Worst-case estimates of exposure in the immediate vicinity of the largest emitter in Canada, which are likely 10- to 100-fold greater than those anticipated under most

conditions, do not appreciably exceed a Tolerable Concentration derived on the basis of increases in serum hepatic enzymes in exposed workers. A Tolerable Concentration is the level to which it is believed a person may be exposed daily over a lifetime without deleterious effect.

Based on available data, it is concluded that N,N-dimethylformamide is not entering the environment in a quantity or concentration or under conditions that (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity, (b) constitute or may constitute a danger to the environment on which life depends or (c) constitute or may constitute a danger in Canada to human life or health. Therefore, N,N-dimethylformamide is not considered to be "toxic" as defined in Section 64 of the *Canadian Environmental Protection Act, 1999* (CEPA 1999).

The evaluation of options under CEPA 1999 to reduce exposure to DMF is not considered to be a priority at this time. However, this is based upon current use patterns; thus, future releases of this compound should continue to be monitored to ensure that exposure does not increase to any significant extent.

1.0 INTRODUCTION

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the federal Ministers of the Environment and of Health to prepare and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" or capable of becoming "toxic" as defined in Section 64 of the Act, which states:

> ...a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
> (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
> (b) constitute or may constitute a danger to the environment on which life depends; or
> (c) constitute or may constitute a danger in Canada to human life or health.

Substances that are assessed as "toxic" as defined in Section 64 may be placed on Schedule I of the Act and considered for possible risk management measures, such as regulations, guidelines, pollution prevention plans or codes of practice to control any aspect of their life cycle, from the research and development stage through manufacture, use, storage, transport and ultimate disposal.

Based on initial screening of readily accessible information, the rationale for assessing N,N-dimethylformamide (DMF) provided by the Ministers' Expert Advisory Panel on the Second Priority Substances List (Ministers' Expert Advisory Panel, 1995) was as follows:

> DMF is used as a solvent in the production of resins and polar polymers. Applications include protective coatings, adhesives, films, printing inks, capacitors and electroplating. DMF is likely to be released from industrial and consumer uses. It does not break down easily in air. It is toxic to the liver in both humans and animals, and is possibly carcinogenic to humans. An assessment is required to evaluate whether it poses a risk to human health and the environment in Canada.

Descriptions of the approaches to assessment of the effects of Priority Substances on the environment and human health are available in published companion documents. The document entitled "Environmental Assessments of Priority Substances under the *Canadian Environmental Protection Act.* Guidance Manual Version 1.0 — March 1997" (Environment Canada, 1997a) provides guidance for conducting environmental assessments of Priority Substances in Canada. This document may be purchased from:

> Environmental Protection Publications
> Environmental Technology Advancement Directorate
> Environment Canada
> Ottawa, Ontario
> K1A 0H3

It is also available on the Commercial Chemicals Evaluation Branch web site at www.ec.gc.ca/cceb1/ese/eng/esehome.htm under the heading "Guidance Manual." It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which will be addressed in future releases of the guidance manual for environmental assessments of Priority Substances.

The approach to assessment of effects on human health is outlined in the following publication of the Environmental Health Directorate of Health Canada: "*Canadian Environmental Protection Act* — Human Health Risk Assessment for Priority Substances" (Health

Canada, 1994), copies of which are available from:

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

or on the Environmental Health Directorate publications web site (www.hc-sc.gc.ca/ehp/ehd/catalogue/bch.htm). The approach is also described in an article published in the *Journal of Environmental Science and Health — Environmental Carcinogenesis & Ecotoxicology Reviews* (Meek *et al.*, 1994). It should be noted that the approach outlined therein has evolved to incorporate recent developments in risk assessment methodology, which are described on the Environmental Substances Division web site (www.hc-sc.gc.ca/ehp/ehd/bch/env_contaminants/psap/psap.htm) and which will be addressed in future releases of the approach paper for the assessment of effects on human health.

The search strategies employed in the identification of data relevant to assessment of potential effects on the environment (prior to September 1999) and on human health (prior to February 2000) are presented in Appendix A. Review articles were consulted where appropriate. However, all original studies that form the basis for determining whether DMF is "toxic" under CEPA 1999 have been critically evaluated by staff of Environment Canada (entry and environmental exposure and effects) and Health Canada (human exposure and effects on human health).

Preparation of the environmental components of the assessment was led by A. Chevrier and M. Lewis with support from H. Atkinson, K. Doe and B. Scott under the direction of P. Thompson and P. Doyle. Sections of the Assessment Report and the supporting documentation related to the environmental assessment of DMF (Environment Canada, 2000) were reviewed by the Environmental Resource Group, established by Environment Canada to support the environmental assessment:

D. Andrews, Golder Associates Ltd.
N. Bunce, University of Guelph
B. Elliott, Environment Canada
R. Gensemer, Boston University
M. Mumtaz, Chinook Group Ltd.
C. Nalewajko, University of Toronto
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J. Prinsen, Environment Canada
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Environmental sections of the Assessment Report and the supporting documentation were also reviewed by:

K. Bolton, University of Toronto
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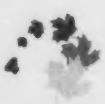
S. Mabury, University of Toronto
M. Sheppard, EcoMatters Inc.

Sections of this Assessment Report related to health and the relevant supporting documentation (Health Canada, 2000) were prepared, based, in part, on background information prepared in 1999 by BIBRA International (1999), by the following staff of Health Canada:

R. Gomes
G. Long
M.E. Meek
M. Walker

Sections of the Assessment Report and supporting documentation on genotoxicity were reviewed by D. Blakey of the Environmental and Occupational Toxicology Division of Health Canada.

In the first stage of external review, sections of the supporting documentation pertaining to human health were considered, primarily to address adequacy of coverage, by



G.L. Kennedy, DuPont Haskell Laboratory for Toxicology and Industrial Medicine.

Accuracy of reporting, adequacy of coverage and defensibility of conclusions with respect to hazard characterization and dose–response analyses were considered at a panel meeting of the following members, convened by Toxicology Excellence in Risk Assessment (TERA), on February 14, 2000, in Ottawa, Ontario:

M.S. Abdel-Rahman, University of Medicine and Dentistry of New Jersey
C. Abernathy, U.S. Environmental Protection Agency
J.P. Christopher, California Environmental Protection Agency
J.C. Collins, Solutia, Inc.
J.T. Colman, Syracuse Research Corporation
M. Mumtaz, Agency for Toxic Substances and Disease Registry
K.A. Poirier, TERA
J.E. Whalen, U.S. Environmental Protection Agency

The health-related sections of the Assessment Report were reviewed and approved by the Health Protection Branch Risk Management meeting of Health Canada.

The entire Assessment Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

A draft of the Assessment Report was made available for a 60-day public comment period (June 3 to August 2, 2000) (Environment Canada and Health Canada, 2000). Following consideration of comments received, the Assessment Report was revised as appropriate. A summary of the comments and responses is available on the Internet at:

www.ec.gc.ca/cceb1/eng/final/index_e.html

The text of the Assessment Report has been structured to address environmental effects initially (relevant to determination of "toxic" under Paragraphs 64(a) and (b)), followed by effects on human health (relevant to determination of "toxic" under Paragraph 64(c)).

Copies of this Assessment Report are available upon request from:

Inquiry Centre
Environment Canada
Main Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or on the Internet at:

www.ec.gc.ca/cceb1/eng/final/index_e.html

Unpublished supporting documentation, which presents additional information, is available upon request from:

Commercial Chemicals Evaluation Branch
Environment Canada
14th Floor, Place Vincent Massey
351 St. Joseph Blvd.
Hull, Quebec
K1A 0H3

or

Environmental Health Centre
Room 104
Health Canada
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

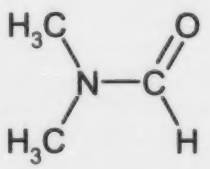
2.0 Summary of Information Critical to Assessment of "Toxic" under CEPA 1999

2.1 Identity and physical/chemical properties

N,N-Dimethylformamide (CAS No. 68-12-2) is a colourless liquid at room temperature with a faint amine odour (BUA, 1994). Many synonyms are used to identify this compound (Figure 1), the most common being the acronym DMF. The molecular weight of DMF is 73.09, as calculated from its empirical formula (C_3H_7NO). The DMF sold commercially contains trace amounts of methanol, water, formic acid and dimethylamine (BUA, 1994).

Figure 1 Chemical structure and identity of N,N-dimethylformamide (DMF)

IUPAC name: N,N-Dimethylformamide
Chemical family: amide



Synonyms: DMF, DMFA, DMF-DMA, Formdimethylamide, Formic acid dimethyl amide, Formyl dimethylamide, N,N-Dimethyl formic acid amide, N-Formyldimethylamine, Dimethylacetal, Formic acid amide, N,N-dimethyl, N,N-Dimethylmethanamide (Anonymous, 1981; SRC, 1988; Gescher, 1990; WHO, 1991; BUA, 1994; CCOHS, 1997a,b)

DMF is miscible in all proportions with water and most organic solvents (SRC, 1988; Gescher, 1990; BUA, 1994; SRI International, 1994). It is also a powerful solvent for a variety of organic, inorganic and resin products (SRI International, 1994). At temperatures below 100°C, DMF is not readily photooxidized (BUA, 1994). Temperatures in excess of 350°C are required for DMF to decompose into carbon monoxide and dimethylamine (Farhi *et al.*, 1968; Bunce, 1998a).

Some important physical and chemical properties of DMF are summarized in Table 1. A vapour pressure of 490 Pa was estimated by Riddick *et al.* (1986). Because DMF is a miscible compound, it is preferable to determine the Henry's law constant experimentally; however, no experimental data were found in the literature. Estimates of the Henry's law constant were 0.0075 and 0.0345 Pa·m³/mol (BUA, 1994; Bobra, 1999). It is important to note that due to the complete miscibility and low vapour pressure of DMF, the calculated Henry's law constants are very uncertain (DMER and AEL, 1996; Bobra, 1999). The octanol/water partition coefficient (log K_{ow} = –1.01) was determined by a shake flask experiment (Hansch *et al.*, 1995).

2.2 Entry characterization

2.2.1 Production, importation, exportation and use

DMF has been termed the universal organic solvent and is widely used where a low rate of evaporation is required (Howard, 1993). With a worldwide production capacity estimated at 225 000 tonnes per year, DMF is reportedly used in large volumes throughout the world (Eberling,

TABLE 1 Physical and chemical properties of DMF

Chemical property	Value	Reference	Values used in fugacity calculations
Molecular weight	73.09		73.09
Vapour pressure (Pa at 25°C)	490	Riddick *et al.*, 1986	490
Solubility (g/m^3)	Miscible	BUA, 1994	1.04×10^6
Log K_{ow}	–1.01	Hansch *et al.*, 1995	–1.01
Henry's law constant	0.0345	Bobra, 1999	0.0345
(Pa·m^3/mol at 25°C)	0.0075	BUA, 1994	
Density/specific gravity (g/mL at 25°C)	0.9445	WHO, 1991	
Melting point (°C)	–60.5	WHO, 1991	–60.5
Boiling point (°C)	153.0	WHO, 1991	
Half-life in air (hours)	~192	Estimated from propane	170
Half-life in water (hours)	18	Dojlido, 1979	55
	36	Ursin, 1985	
Half-life in soil (hours)	Assumed to be equivalent to that in water		55
Half-life in sediment (hours)	–		170
Half-life in suspended sediment (hours)	–		55
Half-life in fish (hours)	–		55
Half-life in aerosol (hours)	–		5

1980; Anonymous, 1981; Gescher, 1990; Marsella, 1994). The Canadian production capacity is less than 10 000 tonnes annually, representing less than 5% of the world production (Eberling, 1980; Marsella, 1994; SRI International, 1994). The only Canadian producer of DMF is located in Ontario (Eberling, 1980; Marsella, 1994; SRI International, 1994). The Canadian market for DMF is quite small, with an estimated domestic consumption in the range of less than 1000 tonnes per year (SRI International, 1994; Environment Canada, 1998). In 1996, the majority of industries using DMF were located in Ontario and Quebec (Environment Canada, 1998). However, the largest total quantity used in a province was reported for Manitoba (390 tonnes). Quebec facilities used approximately 175 tonnes in 1996, while Ontario industries reported using only 74 tonnes. Less than 50 tonnes of DMF were used in other Canadian provinces.

In 1996, 13 facilities imported approximately 2500 tonnes of DMF into Canada. The majority of DMF produced in or imported into Canada is subsequently exported to the United States (SRI International, 1994; Environment Canada, 1998). In 1996, most of this import–export activity occurred between U.S. companies and Canadian facilities located in central Canada (Environment Canada, 1998).

Pesticide manufacture accounts for the greatest percentage use of DMF in Canada, with 441 tonnes (66%) used for this purpose in 1996 (Environment Canada, 1998). DMF is present as a formulant in fungicides, in slimicides used in closed systems in pulp and paper mills, and in plant growth regulators registered in Canada, at concentrations ranging from 4.5% to 40.2% (Moore, 1999). The use of DMF as a pesticide is

not considered in this assessment, as it is regulated under the *Pest Control Products Act* and Regulations.

The Canadian oil and gas/petrochemical sector dominated the industrial uses of DMF in 1996, accounting for a total of 141 tonnes (22%) (Environment Canada, 1998). DMF is used in this sector primarily for the separation of gas streams. Other major reported uses of DMF included chemical aid in relation to dyes and pigments (11 tonnes) and pharmaceuticals (21 tonnes) and degreaser/cleaner in various industrial applications (32 tonnes) (Environment Canada, 1998).

Minor uses of DMF accounted for approximately 1% of the reported quantity of DMF used in 1996 and were related to the manufacture of leather and fabric, the formulation of paints and paint remover, the coating for polyvinyl chloride (PVC), and the manufacture of polyresin, sealant and adhesive (Environment Canada, 1998).

In 1996, a number of companies were reportedly involved in the redistribution of DMF to various other industries and laboratories (Environment Canada, 1998). These included 9 primary distributors (>5 tonnes per year) and 17 secondary distributors (5 tonnes per year or less). Many of these distributors were involved in repackaging a total of 15 tonnes of DMF into small containers for the use of laboratories located in hospitals, research institutions or industrial facilities.

2.2.2 *Sources and releases*

2.2.2.1 Natural sources

BUA (1994) identified no known natural sources of DMF. However, DMF is a possible product of the photochemical degradation of dimethylamine and trimethylamine (Pellizzari, 1977; Pitts *et al.*, 1978; U.S. EPA, 1986). Both are commonly occurring natural substances and are also used in industrial applications (European Chemicals Bureau, 1996a,b).

2.2.2.2 Anthropogenic sources

In 1996, just over 16 tonnes of DMF were reportedly released to all environmental media from various industrial locations in Canada, of which 93% (15.079 tonnes) was reported to have been released to the atmosphere and the remainder released to water (0.245 tonnes), wastewater (0.204 tonnes), landfill sites (0.026 tonnes) or deep-well injection (0.669 tonnes) (Environment Canada, 1998). The petrochemical sector was responsible for 84% (12.7 tonnes) of the reported atmospheric releases, essentially all from a single location in southern Quebec. Releases from this location in 1998 were estimated at 10.4 tonnes (Environment Canada, 1998). Releases from the pharmaceutical industry accounted for 87% (0.212 tonnes) of total releases to water. Total release volumes from Canadian industrial sectors include 1.2 tonnes from manufacture of pharmaceuticals, 0.7 tonnes from dye and pigment manufacture, 0.6 tonnes from PVC coating operations, 0.1 tonnes from pesticide manufacture, 0.07 tonnes from paint/finisher and paint remover manufacture, and 0.09 tonnes from other miscellaneous industrial sectors. For 1996, a reported total quantity of 0.056 tonnes was released (0.023 tonnes to air, 0.033 tonnes to water) by the producer during chemical synthesis of DMF (Environment Canada, 1998). Less than 1 tonne of DMF was reportedly released from wastewater treatment facilities and to landfills (Environment Canada, 1998). With a few exceptions, most industries reported little to no seasonal variation in releases (Environment Canada, 1998).

DMF was not one of the top 100 dangerous goods commodities involved in accidents from 1980 to 1994 (Environment Canada, 1997b). Based on the available information, direct releases of DMF to soil (e.g., spill or leakage) appear to be small and infrequent (Environment Canada, 1997b). According to the National Analysis of Trends in Emergencies System (NATES) database, which is a record of accidents involving spills of hazardous materials

in Canada, there were two reported incidents, both occurring in southern Ontario at industrial sites between 1974 and 1997. At one site, 6 kg of DMF were released to the sanitary sewer system due to human error, with no reported environmental effects. The other site released an unknown quantity of DMF from a leaking valve to the ground. Unspecified damage to the aquatic environment was reported (NATES, 1997). Although small accidental releases (e.g., leakage of a storage tank or spill from a barrel) may remain unreported, this information suggests that spills of DMF during use, storage or transport are not a significant route of entry to the environment (Environment Canada, 2000).

The quantity of DMF disposed of at landfill sites is expected to be small. The total quantity of DMF used in formulation of products (other than pesticides) appears to be small in comparison to its use as a manufacturing aid, cleaner or degreaser (Environment Canada, 1998). As such, consumer products deposited in landfill sites should contain little or no DMF. The industrial DMF deposited directly in landfill sites consists primarily of residues remaining after incineration (Environment Canada, 1998).

2.3 Exposure characterization

2.3.1 Environmental fate

The sections below summarize the available information on the distribution and fate of DMF released into the environment.

2.3.1.1 Air

The atmospheric pathway is particularly important in determining exposure to DMF. This is due to the fact that industrial releases of DMF into air appear to be considerably larger than releases to other environmental media (BUA, 1994; Environment Canada, 1998).

Because of the complete miscibility of DMF in water, it is expected that atmospheric DMF can be transported from air into surface water or soil pore water during rain events (DMER and AEL, 1996; Hastie, 1998). Atmospheric DMF should be found in the vapour phase and therefore should be readily available for leaching out by rainfall (U.S. EPA, 1986; Bunce, 1998b). Although the efficiency and rate of washout are unknown, precipitation events (i.e., rain, snow, fog) likely shorten the residence time of DMF in the atmosphere. As water has an atmospheric half-life of approximately 4 days at Canadian latitudes, this can be considered the minimum atmospheric half-life of DMF in relation to precipitation (Hastie, 1998).

Chemical degradation of DMF in air is likely due to reaction with hydroxyl radicals (Hayon *et al.*, 1970). The possibility of direct photochemical decomposition of DMF is extremely small (Grasselli, 1973; Scott, 1998). Other chemical degradation processes — for example, reaction with nitrate radicals — are not known to significantly affect the fate of DMF in air.

Because the reaction rate constant (k_{OH}) for the formamide functional group is unknown, the estimation method proposed by Atkinson (1988) cannot be used to calculate the reactivity of DMF (Atkinson, 1999; Bunce, 1999). However, the degradation half-life of DMF can be roughly estimated by comparing DMF with other compounds in terms of their relative atmospheric reactivity.

Although uncertain, early experimental evidence suggests a low reactivity in air relative to toluene (Laity *et al.*, 1973; U.S. EPA, 1974; Darnall *et al.*, 1976; Bobra, 1999). The maximum rate of nitrogen dioxide formation for DMF was reported to be 0.4 relative to that of toluene in the Laity *et al.* (1973) study. Half-lives as long as 10 days have been calculated for toluene at northern latitudes in the winter (Government of Canada, 1992).

Experiments in smog chambers also suggest a low reactivity for DMF relative to propane (Sickles *et al.*, 1980). The k_{OH} of propane is 1.2×10^{-12} cm^3 per molecule per second (Finlayson-Pitts and Pitts, 1986). Using the global average hydroxyl radical concentration of 7.7×10^5 molecules/cm^3 (Prinn *et al.*, 1987) and the calculation method proposed by Atkinson (1988), the half-life of propane is estimated at approximately 8 days.

Although the degradation half-life of DMF in air cannot be estimated with certainty, the available evidence suggests that it is at least 8 days (192 hours). The mean half-life used for fugacity-based fate modelling (Section 2.3.1.4) was 170 hours, as it is frequently used to represent a half-life range of 100–300 hours (DMER and AEL, 1996). This half-life may be underestimated; however, sensitivity analysis on the fugacity-based results indicates that partitioning estimates are not sensitive to this parameter, but estimated concentrations are affected (Bobra, 1999).

2.3.1.2 Surface water and sediment

Once released into surface water, DMF is unlikely to transfer to sediments, biota or the atmosphere. With a log K_{ow} of –1.01 (Hansch *et al.*, 1995), DMF remains in the dissolved aquatic form and is not expected to adsorb to the organic fraction of sediments or suspended organic matter. This K_{ow} also suggests that DMF does not concentrate in aquatic organisms (BUA, 1994); indeed, no bioaccumulation was observed in carp during an 8-week bioaccumulation test (Sasaki, 1978). Estimated Henry's law constants suggest that volatilization from water will be slight (BUA, 1994; Bobra, 1999).

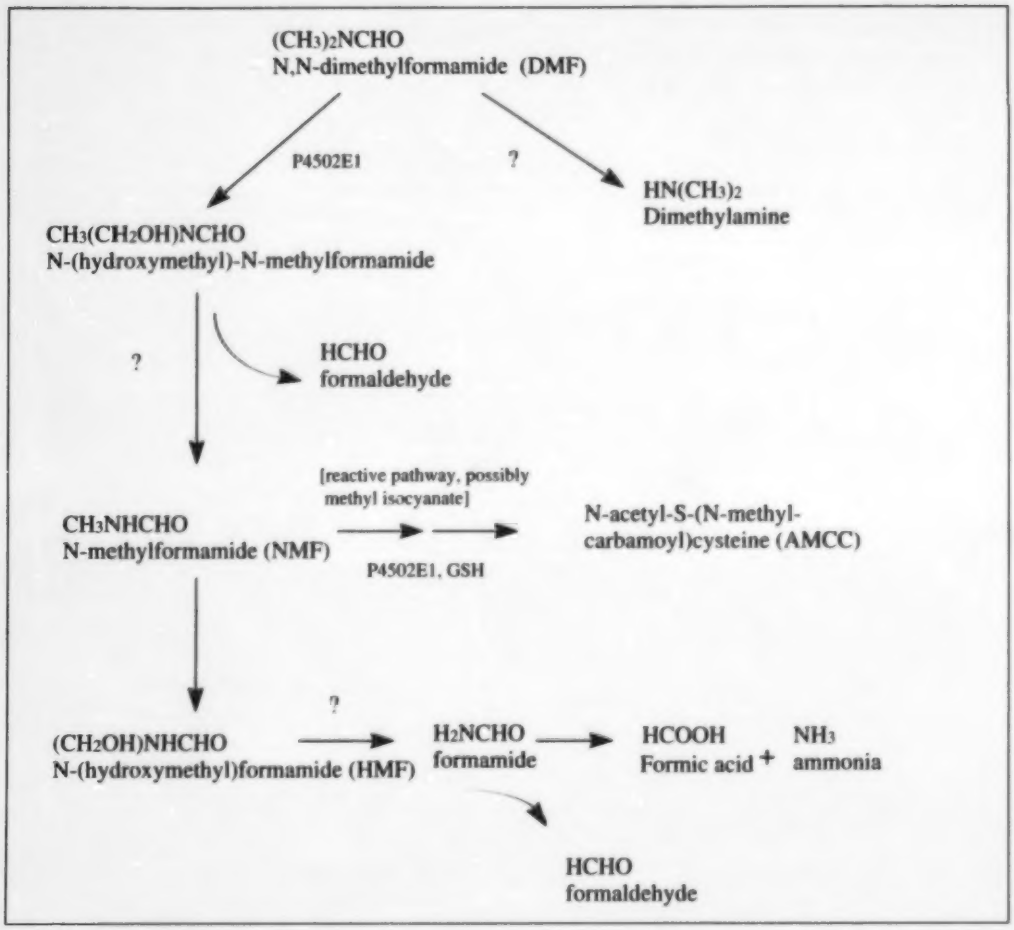
The overall rate of chemical degradation in surface water is expected to be very slow relative to biodegradation. Photochemical decomposition is unlikely in water (Grasselli, 1973; U.S. EPA, 1986). The photooxidation half-life of DMF in water was estimated experimentally at 50 days and would be even longer in the natural environment where other compounds compete for reaction with hydroxyl radicals (Hayon *et al.*, 1970). The rate of hydrolysis of amides like DMF at normal temperatures in laboratory studies is extremely slow even under strong acid or base conditions (Fersht and Requena, 1971; Eberling, 1980). The relatively low temperature (generally less than 20°C) and near-neutral pH of natural surface water therefore limit and almost preclude the hydrolysis of DMF under normal environmental conditions (Frost and Pearson, 1962; Langlois and Broche, 1964; Scott, 1998).

Biodegradation appears to be the primary degradation process in surface water. Under experimental conditions, DMF was degraded, either aerobically or anaerobically, by various microorganisms and algae in activated sludges, over a wide range of concentrations (Hamm, 1972; Begert, 1974; Dojlido, 1979; Chromek *et al.*, 1983; Ursin, 1985; Stronach *et al.*, 1987). Intermediate biodegradation products include formic acid and dimethylamine, which further degrade to ammonia, carbon dioxide and water (Dojlido, 1979; Scott, 1998) (see Figure 2).

Biodegradation of DMF in receiving surface waters is unlikely to be affected by the inherent toxicity of DMF and its biodegradation products. Concentrations above 500 mg/L in effluent were shown to reduce the efficiency of treatment systems using activated sludge (Thonke and Dittmann, 1966; Nakajima, 1970; Hamm, 1972; Begert, 1974; Carter and Young, 1983). However, even with continuous releases, such high concentrations of DMF are not anticipated in natural waters.

Biodegradation half-lives have been measured in the range of 18–36 hours (Dojlido, 1979; Ursin, 1985). No information is available on the half-life of DMF in sediments. DMER and AEL (1996) recommend a sediment half-life of 170 hours based on the assumption that reactivity in sediment is slower than in soil.

FIGURE 2 Biotransformation of DMF (adapted from WHO, 1991; Gescher, 1993)



2.3.1.3 Soil and groundwater

Fugacity-based fate modelling and the miscibility of DMF suggest that some of the DMF released into the atmosphere can reach the ground, at least in part through rainfall (DMER and AEL, 1996; Beauchamp, 1998; Bobra, 1999). Once in soils, DMF will be degraded by chemical and biological processes or leached into groundwater.

As rain fills the available pore space in soils, DMF is incorporated into the pore water. With a log K_{ow} of –1.01 (Hansch *et al.*, 1995), DMF will not tend to adsorb to humic material. Weak bonds with the mineral phase are possible but likely insignificant because of the high solubility of DMF (Bolton, 1998).

Biological degradation and, to a lesser extent, chemical processes operating in surface water would also likely affect DMF contained in soil pore water (Scott, 1998). As for surface

water, biodegradation should therefore be the primary breakdown mechanism in soils. A soil bacterial culture acclimated to small amounts of petroleum and petroleum products degraded DMF under aerobic conditions within 18 hours (Romadina, 1975), suggesting a soil biodegradation half-life similar to the one observed in water. A somewhat longer conservative half-life of 55 hours was used in fugacity-based fate modelling (DMER and AEL, 1996; Beauchamp, 1998; Bobra, 1999).

The miscibility of DMF and its low estimated Henry's law constant suggest limited volatilization from moist soils (BUA, 1994). However, DMF will be efficiently removed from soils by leaching into groundwater likely at the same speed as water percolates through the soil (Lesage, 1997). This is supported by a calculated organic carbon/water partition coefficient (K_{oc}) of 7 (Howard, 1993) and a soil sorption coefficient (K_{om}) of about 50, estimated from quantitative structure–activity relationships (Sabljic, 1984; U.S. EPA, 1986), which both suggest that DMF is mobile in soils. If it reaches groundwater, DMF will be subject to slow anaerobic degradation (Lesage, 1997; Scott, 1998).

2.3.1.4 Environmental distribution

Fugacity modelling was conducted to provide an overview of environmental fate from key reaction and advection (movement out of a system) pathways for DMF and its overall distribution in the environment. A steady-state, non-equilibrium model (Level III fugacity model) was run using the methods developed by Mackay (1991) and Mackay and Paterson (1991). Assumptions, input parameters and results are summarized in Environment Canada (2000) and presented in detail in DMER and AEL (1996), Beauchamp (1998) and Bobra (1999). Modelling predictions do not reflect actual expected concentrations in the environment but rather indicate the broad characteristics of the fate of the substance in the environment and its general distribution among media.

Modelling results identify air as an important exposure medium. If DMF is emitted into air, fugacity modelling predicts that 61% of the chemical will be found in air, 32% in soil and only 7% in water. These results suggest that most of the DMF released into air will remain in that compartment, where it will be degraded by chemical reactions. They also indicate that some atmospheric DMF can reach the aquatic and terrestrial environment — presumably in rain and runoff (Lei, 1998; Scott, 1998). However, the quantity of DMF available for entrainment in rain and runoff is limited by degradation in the atmosphere.

Fugacity modelling also indicates that when DMF is continuously discharged into either water or soil, most of it can be expected to be found in the receiving medium. For example, if it is released into water, 99% of the DMF is likely to be found in the water, and subsequent transport into sediment or bioconcentration in biota is not likely to be significant. When releases are into soil, 94% of the material remains in the soil — presumably in soil pore water (Scott, 1998). Therefore, indirect releases of DMF to air, such as transfers from other environmental media, play only a small role in maintaining levels of DMF in the atmosphere.

It is important to note that fugacity-based partitioning estimates are significantly influenced by input parameters such as the Henry's law constant, which, in this case, is highly uncertain. Therefore, the above partitioning estimates are also uncertain.

2.3.2 Environmental concentrations

No data on concentrations of DMF in ambient air or surface water in Canada were identified, and data on DMF concentrations in Canadian soil and groundwater are very limited.

2.3.2.1 Ambient air

Two Canadian industries report concentrations in stack emissions of less than 7.5 mg/m^3

(Environment Canada, 1998, 1999). Data on concentrations in ambient air in the vicinity of these sources are, however, not available. The highest levels of DMF in air are likely found in the immediate vicinity of the industrial facility in Quebec with the greatest annual releases (13 tonnes per year); however, no atmospheric measurements were available from this location.

In Lowell, Massachusetts (Amster *et al.*, 1983), DMF was detected in the air over an abandoned chemical waste reclamation plant (0.007 mg/m^3), a neighbouring industry (>0.15 mg/m^3) and a residential area (0.024 mg/m^3). Ambient air samples collected in the northeastern United States in 1983 contained DMF at concentrations ranging from <0.000 02 to 0.0138 mg/m^3 (Kelly *et al.*, 1993, 1994). Additional U.S. data collected in 1983 show levels of DMF generally less than 0.02 mg/m^3 at a hazardous waste site in unsettled wind conditions, as high as 8.5 mg/m^3 90 m downwind of a nearby industrial facility and less than 0.02 mg/m^3 in adjoining residential areas within a 0.8-km radius of the site (Clay and Spittler, 1983).

Japan reports a range of 0.000 11–0.0011 mg/m^3, but specific locations and proximity to sources are not provided (Environment Agency Japan, 1996). In Germany, a DMF concentration of ≥0.000 005 mg/m^3 was detected in air (Figge *et al.*, 1987).

2.3.2.2 Surface water and sediment

DMF was detected (detection limit 0.002 mg/L) in only 1 of 204 surface water samples collected between August 1975 and September 1976 from 14 heavily industrialized river basins in the United States (Ewing *et al.*, 1977). The Environment Agency Japan (1996) reports between 0.0001 and 0.0066 mg/L in 18 out of 48 water samples taken in 1991. In addition, 24 water samples collected in 1978 were below the detection limits of 0.01–0.05 mg/L (Environment Agency Japan, 1985). The proximity of these measurements to industrial sources is not known.

Canadian monitoring data are available for effluents at one southern Ontario location, which released less than approximately 0.03 tonnes into surface water in 1996 (Environment Canada, 1998). The facility reported a DMF concentration range of <1–10 mg/L in effluents but has since established a wastewater treatment plant, which reduced effluent concentrations to non-detectable levels (detection limit 0.5 mg/L). DMF was found in 1 of 63 industrial effluents in the United States at a detection limit of 0.01 mg/L (Perry *et al.*, 1979). The U.S. EPA (1999a) quotes an effluent concentration of 0.005 mg/L at a sewage treatment plant in 1975.

The properties of DMF and fugacity modelling results both suggest negligible accumulation of DMF in sediments (BUA, 1994; Hansch *et al.*, 1995; DMER and AEL, 1996; Beauchamp, 1998; Bobra, 1999). However, concentrations of 0.03–0.11 mg/kg were reported in sediments (9 out of 48 samples) in Japan (Environment Agency Japan, 1996). No information is provided on proximity to sources of DMF, sediment characteristics or hydrological regimes. In addition, because information on sampling and analytical methods is not provided, the quality of these data cannot be assessed. Twenty-four sediment samples collected in 1978 at unspecified locations in Japan were below the detection limits of 0.1–0.3 mg/kg (Environment Agency Japan, 1985).

2.3.2.3 Soil and groundwater

In 3 of 23 groundwater samples collected in the United States, concentrations ranged from 0.05 to 0.2 mg/L, with an average concentration of 0.117 mg/L (SRC, 1988; U.S. EPA, 1999a). Of the 10 samples collected at wells in southern Ontario, only 1 sample contained detectable levels of DMF (detection limit 0.001 mg/L); however, the method of analysis employed does not provide reliable quantitative measurements (OMEE, 1996; Lesage, 1998).

The concentrations of DMF in soils may be elevated locally by spills and leakage from storage tanks, particularly in the improbable case of a large spill. Based on the available information, releases of DMF into soils and groundwater in this manner are expected to be insignificant at most locations. This is supported by one data set near a facility in southern Ontario, which indicates non-detectable levels of DMF near storage tanks at a soil depth of 1–4 m (detection limit 1 mg/kg) (Environment Canada, 1999).

2.3.2.4 Drinking water

Although DMF was listed as a contaminant in a survey of drinking water in the United States, quantitative data were not reported (Howard, 1993).

2.3.2.5 Food

Concentrations of DMF in food in Canada or elsewhere were not identified. DMF is not regulated under the Canadian *Food and Drugs Act* (Salminen, 1999).

2.3.2.6 Consumer products

DMF is not a regulated substance under the Consumer Chemicals and Containers Regulations of Canada's *Hazardous Products Act* (Chowhan, 1999).

2.3.2.7 Multimedia study

A Health Canada-sponsored multimedia exposure study for DMF and other volatile organic compounds (VOCs) was conducted in two stages during 1996 and 1997. Initially, a pilot study of 44 homes was conducted in the Greater Toronto area in Ontario (Otson and Meek, 1996). Subsequently, a second phase, involving 50 homes, was conducted in the Greater Toronto area, Nova Scotia and Alberta (Conor Pacific Environmental, 1998). DMF was not detected in samples of outdoor, indoor or personal air, tap water or composite food samples.

DMF was not detected in indoor air samples from the 50 residences in phase 2 (detection limit 3.4 $\mu g/m^3$). It was also not detected in tap water samples from phase 2 of the study, although the limit of detection was high (0.34 µg/mL). DMF was not recovered reproducibly in composite food or beverage samples in this study.

2.4 Effects characterization

2.4.1 Ecotoxicology

DMF has been the focus of several toxicity studies conducted on a range of species (see Table 2). The most sensitive endpoints found for terrestrial and aquatic organisms are presented below. More extensive descriptions of environmental effects are provided in several reviews (U.S. EPA, 1986; SRC, 1988; WHO, 1991; BUA, 1994; Environment Canada, 2000).

2.4.1.1 Aquatic organisms

A number of studies are available for a range of taxa, including protozoa, blue-green algae, diatoms, green algae, macrophytes, molluscs, oligochaetes, crustaceans, insect larvae and fish.

For four species of fish, EC_{50} and LC_{50} values ranged from approximately 7100 to 12 000 mg/L (Batchelder, 1976; Johnson and Finley, 1980; Call *et al.*, 1983; Poirier *et al.*, 1986; Groth *et al.*, 1994). The most sensitive fish species appears to be the bluegill (*Lepomis macrochirus*), with an LC_{50} of 7100–7500 mg/L.

Aquatic invertebrates tested include the water flea, *Daphnia magna*, and various species of insect larvae. The water flea appears to be the most sensitive invertebrate, with a chronic No-Observed-Effect Level (NOEL) of 1140 mg/L following 28 days' exposure (Leblanc and Surprenant, 1983). Acute endpoints (48-hour EC_{50} and LC_{50}) for *Daphnia magna* range from 12 400 to 15 700 mg/L, whereas chronic studies (21–28

TABLE 2 Toxicity of DMF to environmentally relevant organisms

Test species	Latin name	Endpoint	Range	References
Bacteria	*Vibrio fischeri*	5-minute EC_{50} light production	20 000 mg/L	Curtis *et al.*, 1982
Bacteria	*Vibrio fischeri*	15-minute IC_{50} light inhibition	13 260–14 830 mg/L	Harwood, 1997a,b
		15-minute IC_{25} light inhibition	5830–6730 mg/L	
Protozoan	*Paramecium caudatum*	4-hour LC_{50} mortality	20 465 mg/L	Rajini *et al.*, 1989
Protozoan	*Spirostomum ambiguum*	24-hour EC_{50} deformations	9870 mg/L	Nalecz-Jawecki and Sawicki, 1999
		24-hour LC_{50} mortality	31 700 mg/L	
		48-hour EC_{50} deformations	8190 mg/L	
		48-hour LC_{50} mortality	19 700 mg/L	
Blue-green algae	*Nostoc* sp.	10–14-day EC_{50} growth inhibition test	<480 mg/L	Stratton, 1987
Blue-green algae	*Anabaena* sp.	10–14-day EC_{50} growth inhibition test	<480 mg/L	Stratton, 1987
Blue-green algae	*Anabaena cylindrica*	10–14-day EC_{50} growth inhibition test	<480 mg/L	Stratton, 1987
Blue-green algae	*Anabaena variabilis*	10–14-day EC_{50} growth inhibition test	<480 mg/L	Stratton, 1987
Blue-green algae	*Anabaena inaequalis*	10–14-day EC_{50} growth inhibition test	5700 mg/L	Stratton, 1987
Blue-green algae	*Anabaena flos-aquae*	48-hour IC_{25} growth inhibition	15 100 mg/L	Peterson *et al.*, 1997
Blue-green algae	*Microcystis aeruginosa*	48-hour IC_{25} growth inhibition	7000 mg/L	Peterson *et al.*, 1997
Blue-green algae	*Oscillatoria* sp.	48-hour IC_{25} growth inhibition	10 400 mg/L	Peterson *et al.*, 1997
Diatom	*Nitzschia* sp.	48-hour IC_{25} growth inhibition	6200 mg/L	Peterson *et al.*, 1997
Green algae	*Selenastrum capricornutum*	48-hour IC_{25} growth inhibition	7700 mg/L	Peterson *et al.*, 1997
Green algae	*Selenastrum capricornutum*	72-hour IC_{25} growth as cell numbers	3420–6280 mg/L	Harwood, 1997a,c
Green algae	*Selenastrum capricornutum*	growth at day 4	Inhibition at 5000 mg/L	El Jay, 1996
Green algae	*Selenastrum capricornutum*	growth at day 4	Stimulation at 1000 mg/L	El Jay, 1996
Green algae	*Chlorella vulgaris*	growth at day 4	Inhibition at 10 000 mg/L	El Jay, 1996
Green algae	*Chlorella vulgaris*	growth at day 4	Stimulation at 1000 mg/L	El Jay, 1996
Green algae	*Chlorella pyrenoidosa*	10–14-day EC_{50} reduction in growth	8900 mg/L	Stratton and Smith, 1988
Duckweed	*Lemna minor*	7-day IC_{25} growth inhibition	4900 mg/L	Peterson *et al.*, 1997
Water flea	*Daphnia magna*	Acute 48-hour EC_{50} immobilization	14 500 mg/L	Poirier *et al.*, 1986
Water flea	*Daphnia magna*	Acute 48-hour EC_{50} survival and mortality	15 700 mg/L	Adams and Heidolph, 1985

TABLE 2 (continued)

Test species	Latin name	Endpoint	Range	References
Water flea	*Daphnia magna*	Acute 48-hour LC_{50} mortality	14 400 mg/L	Ziegenfuss *et al.*, 1986
Water flea	*Daphnia magna*	Acute 48-hour LC_{50} mortality	14 530 mg/L	Call *et al.*, 1983
Water flea	*Daphnia magna*	Acute 48-hour EC_{50} immobilization	13 100 mg/L	Sebaugh *et al.*, 1991
Water flea	*Daphnia magna*	Chronic 21-day EC_{50} survival and mortality	3721 mg/L	Adams and Heidolph, 1985
Water flea	*Daphnia magna*	Chronic 21-day NOEC/LOEC survival and mortality	1500–3000 mg/L	Adams and Heidolph, 1985
Water flea	*Daphnia magna*	Chronic 28-day NOEL survival and mortality	1140 mg/L	Leblanc and Surprenant, 1983
Water flea	*Daphnia magna*	Acute 48-hour EC_{50} survival and mortality	12 400 mg/L	Leblanc and Surprenant, 1983
Insect larvae	*Paratanytarsus parthenogeneticus*	48-hour EC_{50}	36 200 mg/L	Poirier *et al.*, 1986
Insect larvae	*Tanytarsus dissimilis*	48-hour LC_{50}	36 000 mg/L	Call *et al.*, 1983
Insect larvae	*Chironomus tentans*	Acute 48-hour LC_{50} mortality	33 500 mg/L	Ziegenfuss *et al.*, 1986
Shrimp	*Crangon crangon*	48-hour LC_{50}	>100 mg/L	Portmann and Wilson, 1971
Rainbow trout	*Oncorhynchus mykiss*	Acute 96-hour LC_{50} mortality	9800–12 000 mg/L	Johnson and Finley, 1980; Call *et al.*, 1983; Poirier *et al.*, 1986
Zebra fish	*Brachydanio rerio*	Acute 96-hour LC_{50} mortality	8840 mg/L	Groth *et al.*, 1994
Fathead minnow	*Pimephales promelas*	Acute 96-hour LC_{50} mortality	9080–11 400 mg/L	Batchelder, 1976; Call *et al.*, 1983; Poirier *et al.*, 1986
Bluegill	*Lepomis macrochirus*	Acute 96-hour LC_{50} mortality	7100–7500 mg/L	Call *et al.*, 1983; Poirier *et al.*, 1986
Soil fungi	*Sclerotinia homeocarpa*	EC_{50} inhibition of fungal growth, as compared with a control growth of 50–70 mm	4840 mg/L	Stratton, 1985
Soil fungi	*Pythium ultimum*	EC_{50} inhibition of fungal growth, as compared with a control growth of 50–70 mm	10 250 mg/L	Stratton, 1985
Soil fungi	*Pestalotia* sp.	EC_{50} inhibition of fungal growth, as compared with a control growth of 50–70 mm	5970 mg/L	Stratton, 1985
Wheat and bean seeds		Inhibition of germination	50 000 mg/L	Szabo, 1972

days' exposure) provide endpoints for mortality between 1140 and 3721 mg/L (Call *et al.*, 1983; Leblanc and Surprenant, 1983; Adams and Heidolph, 1985; Poirier *et al.*, 1986; Ziegenfuss *et al.*, 1986; Sebaugh *et al.*, 1991). The 48-hour LC_{50}s obtained for various species of insect larvae were much higher and ranged from 33 500 to 36 200 mg/L (Call *et al.*, 1983; Poirier *et al.*, 1986; Ziegenfuss *et al.*, 1986).

The most sensitive alga appears to be *Selenastrum capricornutum*, with an IC_{25} for growth inhibition ranging from 3420 to 7700 mg/L (Harwood, 1997a; Peterson *et al.*, 1997). Results for two other green algae species range from 8900 to 10 000 mg/L (Stratton and Smith, 1988; El Jay, 1995). Peterson *et al.* (1997) obtained an IC_{25} for growth inhibition of 6200 mg/L for the diatom *Nitzschia* sp. In the same study, blue-green algae appeared to be the least sensitive, with IC_{25}s for growth inhibition ranging from 7000 to 15 100 mg/L for three tested species (Peterson *et al.*, 1997), a finding that differs from earlier data (Stratton, 1987). Because of the high degree of quality assurance/quality control associated with the Peterson *et al.* (1997) study, these data are considered as definitive levels of toxicity to blue-green algae.

Rajini *et al.* (1989) measured the lethal response of the ciliated protozoan, *Paramecium caudatum*, to acute (4-hour) exposures to DMF. The 4-hour LC_{50} was found to be 20 465 mg/L. A recent paper reports EC_{50}s (deformations) of 8190–9870 mg/L and LC_{50}s of 19 700–31 700 mg/L for the protozoan, *Spirostomum ambiguum* (Nalecz-Jawecki and Sawicki, 1999).

Marine organisms tested include the bacterium, *Vibrio fischeri*, and the common shrimp, *Crangon crangon*. For the decrease in luminescence in *Vibrio fischeri*, the 5-minute EC_{50} value of 20 000 mg/L was reported by Curtis *et al.* (1982) and Kaiser and Palabrica (1991) and is in the same order of magnitude as the 15-minute IC_{50} values of 13 260–14 830 mg/L reported from four tests by Harwood (1997b). IC_{25} values calculated by Harwood (1997a) with the same data set ranged from 5830 to 6730 mg/L. Portmann and Wilson (1971) reported a 48-hour LC_{50} of >100 mg/L for the common shrimp, *Crangon crangon*.

2.4.1.2 Terrestrial organisms

There is little information available on the toxicity of DMF to terrestrial vascular plants. Szabo (1972) found that DMF did not inhibit germination of wheat and bean seeds at 1% (approximately 10 000 mg/L) but did at 5% (approximately 50 000 mg/L); however, little methodological information is provided to permit an assessment of the quality of the data. DMF is included as a component of a systemic seed protectant applied in Canada to seeds of wheat, barley, oats, rye and flax at rates from 0.9 to 1.5 g/kg seed, from a 380 000 mg/L solution. At these concentrations, seed germination is not expected to be adversely affected when seed is properly stored (PMRA, 1999). The IC_{25} of 4900 mg/L for the duckweed (*Lemna minor*), an aquatic angiosperm, also provides an indication that terrestrial angiosperms may not be sensitive to DMF (Peterson *et al.*, 1997). The most sensitive organism in the terrestrial compartment appears to be the soil fungus, *Sclerotinia homeocarpa*, with an EC_{50} of 4840 mg/L for growth inhibition (Stratton, 1985). From the available evidence, it is apparent that plants have a low sensitivity to DMF.

Although no information has been found on the effects of DMF on wildlife, a review of laboratory studies on experimental animals (WHO, 1991) concludes that the acute toxicity of DMF for a variety of species is low. Only one chronic (2-year) inhalation assay was identified in recent literature (Malley *et al.*, 1994). In that study, results for laboratory mice reported a Lowest-Observed-Effect Concentration (LOEC)

of 25 ppm (75 mg/m³)[1] following inhalation of DMF, based on changes in body weight and clinical chemistry (see Section 2.4.3.4.1).

2.4.2 Abiotic atmospheric effects

The potential for DMF to contribute to the depletion of stratospheric ozone, to climate change or to the formation of ground-level ozone was examined.

As DMF is not a halogenated compound, its Ozone Depletion Potential (ODP) is calculated to be 0, and it will therefore not contribute to the depletion of stratospheric ozone (Bunce, 1996).

Gases involved in climate change strongly absorb infrared radiation of wavelengths between 7 and 13 μm, enabling them to trap and re-radiate the Earth's thermal radiation (Wang *et al.*, 1976; Ramanathan *et al.*, 1985). Worst-case calculations were made to determine if DMF has the potential to contribute to climate change (Bunce, 1996), assuming it has the same infrared absorption strength as the reference compound, CFC-11. The Global Warming Potential (GWP) was calculated to be quite small (much less than 1% relative to the reference compound, CFC-11), and DMF is therefore not considered to be involved in climate change (Bunce, 1996; Environment Canada, 2000).

The contribution of VOCs to the formation of ground-level ozone, and the resulting contribution to smog formation, is a complex process and has been studied extensively (e.g., Dann and Summers, 1997). The Photochemical Ozone Creation Potential (POCP) can be calculated based on the hydroxyl radical rate constant; however, the experimental hydroxyl radical rate constant is lacking and can only be estimated. Estimation methods provide an indication that the rate of reaction is rapid, as estimation of the reaction with hydroxyl radicals predicts that the POCP is between 300 and 600 (Bunce, 1997). This would suggest that DMF has a significant potential to contribute to ground-level ozone formation; however, it is important to note that conclusions based on these estimations may be misleading because of the large uncertainties associated with the assumed hydroxyl radical rate constant (Bunce, 1998b).

Ground-level ozone formation is initiated by sunlight and nitrogen oxides. Examination of the relative rate of nitrogen dioxide formation from DMF in a smog chamber was 0.4 relative to that of toluene and very similar to that of acetone (0.3) (Laity *et al.*, 1973). A more recent examination of the potential of DMF to generate ozone was conducted in outdoor smog chamber experiments and indicated that the maximum rate of ozone formation for DMF relative to propane was 0.33, a factor of 4 lower than that of acetone (Sickles *et al.*, 1980). Dann and Summers' (1997) examination of the 117 most abundant hydrocarbon and carbonyl species measured in Canada (DMF not measured) shows propane and acetone to be the 3rd and 11th most abundant urban atmospheric chemicals, respectively; however, propane is ranked 18th and acetone below 30th in terms of their ozone creation potential. This ranking is a function of the atmospheric concentration of the substance and the ratio of the hydroxyl radical rate constant of the chemical of interest to the constant for propylene (Dann and Summers, 1997). The relationship between DMF reactivity and its relative atmospheric concentration provides an indication of DMF's ozone creation potential. In 1996, approximately 4000 tonnes of acetone were reportedly released into the atmosphere (NPRI, 1996), which is about 266 times greater than the total volume of DMF released to the atmosphere (see Section 2.2.1). Based on this information and the reactivity of DMF relative to that of acetone, it is apparent that the potential contribution of DMF to ground-level ozone formation is low.

[1] 1 ppm = 3 mg/m³ (WHO, 1991).

2.4.3 *Experimental animals and* in vitro

2.4.3.1 Acute toxicity

Following oral, dermal, inhalation or parenteral administration, the acute toxicity of DMF in a number of species is low. Lethal doses are generally in the g/kg-bw range for oral, dermal and parenteral routes and in the g/m^3 range for inhalation exposure. Clinical signs following acute exposure include general depression, anesthesia, loss of appetite, loss of body weight, tremors, laboured breathing, convulsions, hemorrhage at nose and mouth, liver injury and coma preceding death. Where protocols included histopathological examination, damage was observed primarily in the liver (WHO, 1991).

2.4.3.2 Irritation and sensitization

IARC (1999), WHO (1991) and Kennedy (1986) reviewed the effects of DMF on the skin and eyes and reported only mild to moderate effects. A single application of neat DMF to the shaved skin of mice at 1–5 g/kg-bw (precise exposure conditions not specified) produced slight transient skin irritation at 2.5–5 g/kg-bw, while similar treatment of rabbits at up to 0.5 g/kg-bw was without effect (Kennedy, 1986; WHO, 1991). Repeated (15- or 28-day) applications of 1–2 g/kg-bw did not induce marked local effects on the skin of rats or rabbits. The instillation of neat or 50% aqueous DMF into the rabbit eye produced moderate corneal injury and moderate to severe conjunctivitis, with some damage still evident 14 days later (Kennedy, 1986; WHO, 1991; IARC, 1999).

2.4.3.3 Short-term and subchronic toxicity

Well-conducted studies in which a comprehensive range of endpoints has been examined are restricted to recent subchronic investigations, the results of which are the focus of the text presented here. While there have been a number of primarily early short-term studies, these have generally been restricted to examination of specific effects following exposure to single dose levels. They are not additionally informative concerning the toxicity of DMF but confirm a range of effects in the liver that, when considered collectively across studies, are consistent with a profile in rats of alterations in hepatic enzymes and increases in liver weight at lowest concentrations and degenerative histopathological changes, cell death and increases in serum hepatic enzymes at higher concentrations. Results of a limited short-term study in monkeys also indicate that this species is less sensitive than rats to the effects of DMF (Hurtt *et al.*, 1991).

In the only short-term investigation in which a dose–response relationship for hepatic effects was characterized, there was a dose-related increase in liver to body weight ratio, significant at all levels of exposure, and in activity of uridine diphosphate glucuronosyl transferase at all levels of exposure in male Wistar rats exposed for 2 weeks via drinking water to approximately 0, 14, 70 or 140 mg/kg-bw per day (Elovaara *et al.*, 1983).

Available data from acute and short-term studies also indicate that there are effects on metabolizing enzymes at very high doses (i.e., 475 mg/kg-bw per day and above administered subcutaneously to rats). These include glutathione metabolism (although reported changes at two different doses were not consistent) and decreases in hepatic microsomal P450 content (Imazu *et al.*, 1992, 1994; Fujishiro *et al.*, 1996).

2.4.3.3.1 Inhalation exposure

The NTP (1992a) carried out a subchronic bioassay in F344 rats, exposing males and females to 0, 50, 100, 200, 400 or 800 ppm (0, 150, 300, 600, 1200 or 2400 mg/m^3) for 6 hours per day, 5 days per week, for 13 weeks. The authors designated 200 ppm (600 mg/m^3) as a No-Observed-Adverse-Effect Level (NOAEL) for both sexes, based upon the absence of histopathological lesions in liver. Minimal to moderate hepatocellular necrosis in both sexes

was observed at 400 and 800 ppm (1200 and 2400 mg/m^3), with the lesion more severe in females. However, in males, both the absolute and relative weights of liver were significantly increased at 100 ppm (300 mg/m^3) and greater, although there was no clear dose–response, as weights declined at the highest dose. Serum cholesterol was increased at all levels of exposure; again, there was no clear dose–response. In males at day 24, there was a dose-related increase in serum alanine aminotransferase (ALT) (significant at all levels of exposure); however, at day 91, the increase was significant only at 400 ppm (1200 mg/m^3). At day 91, there was also a dose-related increase in serum sorbitol dehydrogenase in males (significant at 200 ppm [600 mg/m^3]). In females, relative liver weight was significantly increased at all levels of exposure, with the weight declining at the highest dose. Serum cholesterol was significantly increased at all levels of exposure in females, with no clear dose–response. At day 91, in females, serum sorbitol dehydrogenase and isocitrate dehydrogenase were significantly increased at 200 ppm (600 mg/m^3) and greater.

Craig *et al.* (1984) exposed male and female F344 rats to 0, 150, 300, 600 or 1200 ppm (0, 450, 900, 1800 or 3600 mg/m^3) for 6 hours per day, 5 days per week, for 12 weeks. There were few overt signs of toxicity. Body weight was significantly decreased in both sexes at the highest dose. There were some changes in clinical chemistry and hematological parameters at the highest doses. In males, serum cholesterol was significantly increased at the highest concentration only. Serum alkaline phosphatase (AP) was reduced in a dose-related manner, beginning at 300 ppm (900 mg/m^3). In females, cholesterol was significantly increased at 600 and 1200 ppm (1800 and 3600 mg/m^3). In contrast to males, serum AP was increased in a dose-related manner (significant at the two highest concentrations). Data on organ weights were not presented. Histopathological changes were observed in the liver at the highest doses, were barely discernible at 300 ppm (900 mg/m^3) and were not observed at 150 ppm (450 mg/m^3). The Lowest-Observed-Adverse-Effect Concentration (LOAEC) for both sexes is 300 ppm (900 mg/m^3), based upon slight histopathological changes in the liver (No-Observed-Effect Concentration [NOEC] = 150 ppm [450 mg/m^3]).

B6C3F1 mice were exposed to 0, 50, 100, 200, 400 or 800 ppm (0, 150, 300, 600, 1200 or 2400 mg/m^3) for 6 hours per day, 5 days per week, for 13 weeks (NTP, 1992a). Relative liver weight was significantly increased in both sexes at all levels of exposure, although the dose–response was not clear. Absolute liver weight was significantly increased in females at all dose levels, although the dose–response was not clear. Centrilobular hepatocellular hypertrophy (minimal to mild) was observed in all exposed males and in females at 100 ppm (300 mg/m^3) and higher (LOEC = 50 ppm [150 mg/m^3]).

Craig *et al.* (1984) exposed B6C3F1 mice to 0, 150, 300, 600 or 1200 ppm (0, 450, 900, 1800 or 3600 mg/m^3) for 6 hours per day, 5 days per week, for 12 weeks. Mortality was 10% at 600 ppm (1800 mg/m^3) and 40% at 1200 ppm (3600 mg/m^3). No adverse effects on hematological or clinical chemistry were observed. Hepatic cytomegaly was observed in all exposed mice; the incidence and severity were related to dose (LOEC = 150 ppm [450 mg/m^3]).

Hurtt *et al.* (1992) exposed three male and three female cynomolgus monkeys to 0, 30, 100 or 500 ppm (0, 90, 300 or 1500 mg/m^3) for 6 hours per day, 5 days per week, for 13 weeks. Two males were maintained for a further 13-week observation period after exposure had ceased. The protocol included microscopic examination of a comprehensive range of organ tissues in all animals. Sperm morphology and vaginal cytology were also evaluated in all animals. There were no overt signs of toxicity and no effects on body

weight gain, hematology, clinical chemistry, urinalysis, organ weights or histopathological effects attributable to DMF in cynomolgus monkeys exposed to up to 500 ppm (1500 mg/m^3), leading the authors to conclude that the monkey is much less sensitive than the rat or mouse (Hurtt *et al.*, 1992).

The other inhalation studies are either poorly reported or limited in their scope (Massmann, 1956; Clayton *et al.*, 1963; Cai and Huang, 1979; Arena *et al.*, 1982).

2.4.3.3.2 Oral exposure

In a 90-day dietary study, Crl:CD rats were exposed to 0, 10, 50 or 250 mg/kg-bw per day (Haskell Laboratory, 1960; Kennedy and Sherman, 1986). Mild effects on the liver (enlargement of hepatic cells) and hematological effects (anemia, leukocytosis) were observed at 50 mg/kg-bw per day; at the top dose of 250 mg/kg-bw per day, weight gain was reduced, and the animals had slight anemia, leukocytosis and liver cell enlargement. Although there was an apparent increase in serum cholesterol in both sexes at the highest dose, statistical analyses were not presented. The NOEL was 10 mg/kg-bw per day. The Lowest-Observed-Effect Level (LOEL) is 50 mg/kg-bw per day, based upon a significant increase in relative liver weight in males.

In a second study involving larger group sizes, a different strain (Wistar) and more comprehensive tissue examination, growth was inhibited but no tissue lesions were observed in rats administered DMF in the diet at levels of up to approximately 235 mg/kg-bw per day for 15 weeks (Becci *et al.*, 1983). The LOEL is 69 mg/kg-bw per day, based upon a significant increase in relative liver weight in females at the two highest doses (NOEL = 20 mg/kg-bw per day).

In the corresponding study in CD-1 mice involving dietary administration (males: 0, 22, 70 or 246 mg/kg-bw per day; females: 0, 28, 96 or 326 mg/kg-bw per day) for 17 weeks, there were no overt signs of toxicity and no notable effects on blood morphology, blood biochemistry or urinary parameters (Becci *et al.*, 1983). Microscopic examination of an extensive range of organ tissues revealed only mild effects on the liver in the majority of high-dose males and females. There was a dose-related increase in relative liver weight at all dose levels, although this was statistically significant only in the mid- and high-dose females and in the high-dose males. On this basis, the LOEL is 96 mg/kg-bw per day, based upon a significant increase in relative liver weight in females (NOEL = 28 mg/kg-bw per day).

In a submission to the Office of Toxic Substances of the U.S. Environmental Protection Agency, BASF (1984) reported that there were no adverse effects observed in beagle dogs (four males and four females per group) administered 0, 1.4, 7.0 or 34.8 mg/kg-bw per day (NOEL = 34.8 mg/kg-bw per day) in the diet for 13 weeks. The protocol included measurement of food consumption, body weight gain, hearing tests, ophthalmoscopic examination, clinical laboratory investigations, measurement of organ weights and histopathological observations.

2.4.3.4 Chronic toxicity and carcinogenicity

Presentation in this section is limited to studies in which animals were exposed by inhalation and ingestion. Although there were a few relevant additional investigations in which experimental animals were exposed via injection (Herrold, 1969; Kommineni, 1973), they do not meaningfully contribute additionally to assessment of chronic toxicity or the weight of evidence of carcinogenicity.

2.4.3.4.1 Inhalation exposure

Malley *et al.* (1994) exposed Crl:CD BR rats for 6 hours per day, 5 days per week, to 0, 25, 100 or 400 ppm (0, 75, 300 or 1200 mg/m³) DMF vapour for 24 months. There were no overt signs of toxicity other than a reduction in weight gain in the rats exposed at 400 ppm (1200 mg/m³) and, to a lesser extent and towards the end of the study, in males exposed at 100 ppm (300 mg/m³). Hematological findings were normal, as were urinary analyses. There was a concentration-related increase in serum sorbitol dehydrogenase activity (indicative of hepatic effects) in the male and female rats at 100 and 400 ppm (300 and 1200 mg/m³). Relative liver weights were increased in both sexes at 400 ppm (1200 mg/m³), and microscopic examination revealed hepatic lesions (centrilobular hepatocellular hypertrophy, lipofuscin/hemosiderin accumulation, clear cell foci and single-cell necrosis in males and high-dose females and focal cystic degeneration in males) at 100 and 400 ppm (300 and 1200 mg/m³). Microscopic examination of an extensive range of tissues from the high-dose animals (and of selected tissues from the lower dose groups) revealed no other treatment-related lesions except in females, in which there was an increased incidence of uterine endometrial stromal polyps (1.7%, 5.1%, 3.4% and 14.8% for control, low-, mid- and high-dose females, respectively). Historical control data from the same laboratory indicated a highly variable incidence of endometrial stromal polyps (2–15% for 14 control groups, average 6.6%). The investigators concluded that DMF was not carcinogenic to rats under the conditions of exposure. The LOEC was 100 ppm (300 mg/m³) (NOEC = 25 ppm [75 mg/m³]), based upon a significant increase in centrilobular hepatocellular hypertrophy (both sexes), significant increase in hepatic accumulation of lipofuscin/hemosiderin (both sexes) and hepatic single-cell necrosis (females only).

Mice [Crl:CD 1 (ICR)BR] were exposed to 0, 25, 100 or 400 ppm (0, 75, 300 or 1200 mg/m³) DMF for 6 hours per day, 5 days per week, for 18 months (Malley *et al.*, 1994). Hematological observations were normal. Relative liver weight was significantly increased at the two highest concentrations in males. Microscopic alterations in liver were observed at all levels of exposure. The authors concluded that DMF was not carcinogenic to mice under the conditions of the bioassay. The LOEC is 25 ppm (75 mg/m³), based upon centrilobular hepatocellular hypertrophy (males), hepatic single-cell necrosis (males and females) and hepatic Kupffer cell hyperplasia/pigment accumulation (males).

2.4.3.4.2 Oral exposure

An inadequate carcinogenicity study involving the administration of DMF in the drinking water of BD rats at approximately 10 or 20 mg/kg-bw per day for 500 or 250 days, respectively, provided no evidence of tumour formation, although the extent of tissue examination was not specified (Druckrey *et al.*, 1967). In female Mongolian gerbils administered DMF in the drinking water at concentrations of 1.0–6.6% (around 5–40 mg/kg-bw per day) for up to 200 days, there were many early deaths at concentrations of 1.7% (around 7–11 mg/kg-bw per day) and above, and all DMF-exposed groups had liver degeneration and kidney congestion (Llewellyn *et al.*, 1974).

2.4.3.5 Genotoxicity

The following discussion is limited to results of assays for gene mutation and cytogenesis, i.e., those assays in which the endpoints are most relevant to the assessment of DMF with respect to human health.

The results of assays for gene mutation *in vitro* were almost entirely negative. Of 20 identified assays in *Salmonella*, results were

negative in 18 (Green and Savage, 1978; Purchase *et al.*, 1978; Baker and Bonin, 1981; Brooks and Dean, 1981; Garner *et al.*, 1981; Gatehouse, 1981; Ichinotsubo *et al.*, 1981; MacDonald, 1981; Martire *et al.*, 1981; Nagao and Takahashi, 1981; Richold and Jones, 1981; Rowland and Severn, 1981; Simmon and Shepherd, 1981; Skopek *et al.*, 1981; Venitt and Crofton-Sleigh, 1981; Antoine *et al.*, 1983; Falck *et al.*, 1985; Mortelmans *et al.*, 1986), and 2 had equivocal results (Hubbard *et al.*, 1981; Trueman, 1981). Results in six assays in *Escherichia coli* were all negative (Gatehouse, 1981; Matsushima *et al.*, 1981; Mohn *et al.*, 1981; Thomson, 1981; Venitt and Crofton-Sleigh, 1981; Falck *et al.*, 1985).

Although fewer assays for cytogenetic effects and genotoxicity *in vitro* were identified than for gene mutation, results were also predominantly negative. In assays for chromosomal aberrations (CAs), results were negative for human lymphocytes (Antoine *et al.*, 1983) and Chinese hamster ovary (CHO) (Natarajan and van Kesteren-van Leeuwen, 1981) and weakly positive in human peripheral lymphocytes (Koudela and Spazier, 1979). Results were negative in three mouse lymphoma assays (Jotz and Mitchell, 1981; Mitchell *et al.*, 1988; Myhr and Caspary, 1988) and weakly positive in one (McGregor *et al.*, 1988). Results of *in vitro* tests for sister chromatid exchange (SCE) were negative in three assays in CHO (Evans and Mitchell, 1981; Natarajan and van Kesteren-van Leeuwen, 1981; Perry and Thomson, 1981) and one in human lymphocytes (Antoine *et al.*, 1983). Assays for unscheduled DNA synthesis (UDS) were negative in human fibroblasts (Agrelo and Amos, 1981; Robinson and Mitchell, 1981), mouse hepatocytes (Klaunig *et al.*, 1984) and HeLa cells (Martin and McDermid, 1981); in assays in rat hepatocytes, results were both negative (Ito, 1982) and positive (Williams, 1977). Results of assays for DNA repair in mouse (McQueen *et al.*, 1983) and hamster (McQueen *et al.*, 1983) hepatocytes were also negative. An assay for DNA repair in human hepatocytes had negative results (McQueen *et al.*, 1988).

The database for genotoxicity studies *in vivo* is more limited than that for *in vitro* studies.

In two adequate assays for micronucleus induction, results were negative (Kirkhart, 1981; Antoine *et al.*, 1983). In the latter study, dose levels were too widely spaced, although the top dose is limiting. Results were also negative in two assays in which there were no positive controls (Salamone *et al.*, 1981; Tsuchimoto and Matter, 1981). It should be noted that Salamone *et al.* (1981) observed no effect at doses up to 80% of the LD_{50}. An assay in which an increase in micronuclei was observed in bone marrow of mice was reported only as an abstract (Ye, 1987), although a dose–response was not clear. Although six dose levels were included in the protocol, the highest dose was only 20 mg/kg-bw (oral LD_{50} values in laboratory animals range from 2000 to 7000 mg/kg-bw).

Negative results were reported in assays for chromosomal damage in rats (Sheveleva *et al.*, 1979; McGregor, 1981) and dominant lethal assays in rats (Lewis *et al.*, 1979; McGregor, 1981; Cragin *et al.*, 1990). Limited reporting (abstracts, secondary sources) precluded critical review of these studies.

No abnormalities were observed in sperm in an adequate assay in mice (Antoine *et al.*, 1983). Although negative results were reported in other assays in mice, quantitative data were not presented (Topham, 1980, 1981), or only a secondary source was available (McGregor, 1981).

Quantitative data were not presented in a report of an assay in which SCEs were not observed in bone marrow of mice (Paika *et al.*, 1981).

2.4.3.6 Reproductive and developmental toxicity

2.4.3.6.1 Reproductive toxicity

Effects on organ weights or histopathological effects in the reproductive organs have not been observed in subchronic or chronic studies in rats or mice following inhalation or oral exposure (Becci *et al.*, 1983; Craig *et al.*, 1984; Kennedy and Sherman, 1986; NTP, 1992a; Malley *et al.*, 1994). In several of these subchronic and chronic bioassays, additional reproductive endpoints were examined. These included sperm density, motility or count and length of diestrus in rats and mice exposed for 13 weeks to concentrations up to 800 ppm (2400 mg/m^3) (NTP, 1992a) and semen volume, sperm motility, morphology or count in a limited number of monkeys exposed to 500 ppm (1500 mg/m^3) (Hurtt *et al.*, 1992). In none of these investigations, however, were there adverse effects on reproductive parameters at concentrations or doses less than those at which hepatic effects were observed; indeed, the only effect reported was prolonged diestrus in female rats exposed to 800 ppm (2400 mg/m^3) for 13 weeks (NTP, 1992a).

Few studies were identified in which the protocols were designed specifically to address reproductive toxicity. In a study reported as an abstract (Lewis *et al.*, 1979; Cragin *et al.*, 1990), exposure of male Sprague-Dawley rats to 30 or 300 ppm (90 or 900 mg/m^3) for 6 hours per day for 5 days did not result in histopathological changes in reproductive organs after 6 weeks. Pairing of the exposed males with unexposed females for 6 weeks after exposure resulted in a reduced number of viable fetuses per dam in the low-dose group only.

In a multigeneration study in Swiss mice, DMF was administered in the drinking water at concentrations of 0, 1000, 4000 or 7000 mg/L (NTP, 1992b; Fail *et al.*, 1998). Litters from F0 animals were sacrificed immediately. At week 16, pairs were separated and the final litters reared to postnatal day 21, then entered into an F1 fertility assessment. A crossover mating trial was also carried out with the F0 mice. The lowest level of exposure (1000 mg/L; average 219 mg/kg-bw per day) was designated by the authors as the maximum tolerated dose (LOEL) for the F0 mice, based upon increased relative liver weight in males and females and increased relative kidney and adrenal weights in females. Reproductive effects in F0 mice included reduced fertility and fecundity at 4000 and 7000 mg/L. The crossover trial identified females as the affected sex. Following F1 mating, both F2 litter size and live pup weight were reduced at all doses. At necropsy, body weight of F1 males and females was reduced at the two highest doses, and both absolute and relative liver weights were increased at all doses. The authors concluded that both reproductive and developmental toxicity occurred at the two highest doses (4000 and 7000 mg/L) in the F0 mice and at all dose levels (≥1000 mg/L) in the F1 mice.

2.4.3.6.2 Developmental toxicity

The database on developmental toxicity is more extensive, with numerous studies having been conducted in various species by the inhalation, oral and dermal routes. Emphasis here is on well-conducted and well-reported studies for which protocols and reporting are most extensive.

In studies in which DMF has been administered by inhalation or ingestion, it has been, at most, weakly teratogenic, with malformations being observed only at high doses that were maternally toxic (450 ppm [1350 mg/m^3] by inhalation in rabbits; 503 mg/kg-bw per day following ingestion in rats), based on consideration of maternal body weight and signs of overt toxicity (Hellwig *et al.*, 1991). In general, DMF has induced primarily fetotoxic effects most often at maternally toxic concentrations or doses (100 mg/kg-bw per day by stomach tube in rats) (Saillenfait *et al.*, 1997) but occasionally in the

absence of maternal toxicity, based on determination of body weight gain and overt signs. For example, Lewis *et al.* (1992) reported maternal weight gain in Crl:CD rats at 300 ppm (900 mg/m^3) (maternal LOEC), but not at 30 ppm (90 mg/m^3), at which concentration there was a slight but significant reduction in fetal weight. The mean fetal weights of control, low-dose and high-dose groups were 5.5 ± 0.2, 5.5 ± 0.4 and 5.3 ± 0.2 g, respectively ($p < 0.05$ for both low- and high-dose groups).

The pattern of results of studies by the dermal route was similar, with malformations being observed in rats only at doses that were maternally toxic based on examination of weight gain and overt signs of toxicity only (944 mg/kg-bw per day in rats; 400 mg/kg-bw per day in rabbits; 944 mg/kg-bw per day in mice) (Hellwig *et al.*, 1991). In one of the relatively recent investigations by other authors (Hansen and Meyer, 1990), fetotoxic effects (delayed ossification) only were observed at doses (945 mg/kg-bw per day) at which there were no effects on maternal weight gain and no overt signs of maternal toxicity.

2.4.3.7 Effects on neurological systems

In male Wistar rats exposed to DMF in drinking water for either 2 or 7 weeks, glial cell fractions were isolated from the left cerebral hemisphere and assayed for activity of acid proteinase and 2',3'-cyclic nucleotide 3'-phosphohydrolase (Savolainen, 1981). The right cerebral hemisphere was assayed for RNA, glutathione and activities of succinate dehydrogenase and azoreductase. After 2 weeks of exposure to 0, 7, 35 or 65 mg DMF/kg-bw per day, there was a dose-related increase in activity of 2',3'-cyclic nucleotide 3'-phosphohydrolase, which was significant ($p < 0.001$) at all levels of exposure. After 7 weeks of exposure to 0, 8, 39 or 75 mg/kg-bw per day, the intake of drinking water was significantly reduced at all levels of exposure. There was also a significant reduction in activity of azoreductase and succinate dehydrogenase (uneven dose–response). The authors suggested that formic acid produced during metabolism may have disrupted the cerebral energy metabolism (LOEL = 7–8 mg/kg-bw per day).

2.4.3.8 Immunotoxicity

In a murine local lymph node assay predictive for identification of contact allergens, cell proliferation was significantly increased (based on thymidine incorporation in lymph nodes) in mice (strain not specified) receiving a daily topical application of 25 µL on the dorsum of both ears for 3 consecutive days (Montelius *et al.*, 1996). In subsequent assays, thymidine incorporation in DMF-solvent controls was 1.2–2.8 times higher than in naive mice (Montelius *et al.*, 1998). In contrast, Kimber and Weisenberger (1989) detected no difference in proliferation in a lymph node assay in which lymph node cells from DMF (the solvent)-exposed mice were compared with those from naive mice.

2.4.3.9 Toxicokinetics and metabolism

Following absorption, DMF is uniformly distributed, metabolized primarily in the liver and relatively rapidly excreted as metabolites in urine. The major pathway involves the hydroxylation of methyl moieties, resulting in N-(hydroxymethyl)-N-methylformamide (HMMF), which is the major urinary metabolite in humans and animals (Figure 2). HMMF in turn can decompose to N-methylformamide (NMF). In turn, enzymatic N-methyl oxidation of NMF can produce N-(hydroxymethyl)formamide (HMF), which further degenerates to formamide. An alternative pathway for the metabolism of NMF is oxidation of the formyl group, resulting in N-acetyl-S-(N-methylcarbamoyl)cysteine (AMCC), which has been identified as a urinary metabolite in rodents and humans. A reactive intermediate, the structure of which has not yet been determined (possibly methyl isocyanate), is formed in this pathway; while direct supporting experimental evidence was not identified, this intermediate is suggested to be the putatively toxic metabolite.

Available data in experimental animals indicate that the metabolism of DMF is saturated at high concentrations (100–500 ppm [300–1500 mg/m^3]) (Hundley *et al.*, 1993a,b); at much higher levels (>2000 ppm [>6000 mg/m^3]), DMF may inhibit its own metabolism, based on the results of early studies. Plasma levels of DMF are greater in rats and mice than in monkeys. On repeated exposures, metabolic capacity was increased in rats and mice, although this was not clearly demonstrated in monkeys (Hundley *et al.*, 1993a,b).

Data on interspecies variations in metabolism by the putatively toxic pathway are limited to a few recent studies. In the only investigation in which variations among species were examined (Mráz *et al.*, 1989), the proportion excreted as AMCC was greatest for rats, followed by hamsters and mice. Comparison of these results with those from a study in human volunteers and investigations of occupationally exposed populations indicate that a greater proportion of DMF may be metabolized by the putatively toxic pathway in humans compared with experimental animals. Results of studies in human volunteers are consistent with the hypothesis that the formation of AMCC is preceded by a rate-limiting reversible protein binding of a reactive metabolic intermediate of DMF, possibly methyl isocyanate (Mráz and Nohová, 1992a,b).

There is metabolic interaction between DMF and alcohol, which, although not well understood, is likely due to competitive inhibition of alcohol dehydrogenase.

Angerer *et al.* (1998) reported that hemoglobin from individuals occupationally exposed to DMF contained N-carbamoylated valine residues derived from methyl isocyanate, the likely precursor of AMCC. The metabolism of DMF to HMMF by human liver microsomes *in vitro* has also been demonstrated. The addition of an antibody against rat liver cytochrome P450 2E1 to the incubation mixture strongly inhibited DMF metabolism (Mráz *et al.*, 1993).

2.4.4 *Humans*

Consistent with the results of studies in experimental animals, available data from case reports and cross-sectional studies in occupationally exposed populations consistently indicate that the liver is the target organ for the toxicity of DMF in humans. The profile of effects is consistent with that observed in experimental animals, with related symptoms, increases in serum hepatic enzymes and histopathological effects being reported.

2.4.4.1 Cancer

Data on the incidence of cancer or cancer mortality associated with exposure to DMF are limited to case reports of testicular tumours and single well-conducted and well-reported cohort and case–control studies of occupationally exposed populations (Chen *et al.*, 1988a; Walrath *et al.*, 1989). In the cohort study of 3859 actively employed workers with potential exposure to DMF and to DMF and acrylonitrile (ACN) in a fibre production facility, the incidences of cancer of the buccal cavity/pharynx, lung, prostate, stomach, nervous system and bladder were considered in relation to level of and, for some tumours, duration of exposure and were compared with company and national rates. Level of exposure was classified as low (approximately <10 ppm [<30 mg/m^3]), moderate (sometimes above 10 ppm [30 mg/m^3]) or high, although quantitative data were not reported (Chen *et al.*, 1988a). Women were excluded from analyses because of the small numbers. In an additional case–control study, cancers of the buccal cavity/pharynx (n = 39), liver (n = 6), prostate (n = 43) and testis (n = 11) and malignant melanoma of the skin (n = 39) were reported in approximately 8700 workers from four plants, which included a DMF production plant, two acrylic fibre plants that used DMF as a spinning solvent and a plant using the chemical as a solvent for inks (Walrath *et al.*, 1989).

Three cases of testicular germ cell tumours that occurred during 1981–83 among 153 white men who repaired the exterior surfaces and electrical components of F4 Phantom jets in the United States were reported by Ducatman *et al.* (1986), which led to surveys of two other repair shops at different locations, one in which F4 Phantom jets were repaired and one where other types of aircraft were repaired. Four of 680 workers in the F4 Phantom shop had testicular germ cell cancers (approximately one expected) diagnosed during 1970–83. No cases were reported in the other facility. All seven men had long histories in aircraft repair; although there were many common exposures to solvents in the three facilities, the only one identified as unique to the F4 Phantom jet aircraft repair facilities was to a solvent mixture containing 80% DMF (20% unspecified). Three of the cases had been exposed to this mixture with certainty, and three had probably been exposed. Of the seven cases, five were seminomas and two were embryonal cell carcinomas.

Levin *et al.* (1987) and Frumin *et al.* (1989) reported three cases of embryonal cell carcinoma of the testis in workers at one leather tannery in the United States, where it was reported that DMF as well as a wide range of dyes and solvents were used, including such testicular toxins as 2-ethoxyethanol and 2-ethoxyethanol acetate. The latency period ranged from 8 to 14 years. No additional cancers were reported in a screening effort undertaken to identify additional testicular cancers in 51 of the 83 workers at the leather tannery where the three cases were reported (Calvert *et al.*, 1990).

In an investigation of cancer incidence at a plant producing fibres, compared with company and national rates, there was no increase in the incidence of testicular cancer in 2530 actively employed workers exposed to DMF only. When the data from this cohort were grouped with data from 1329 workers exposed to both DMF and ACN, there was only one case of testicular cancer, compared with 1.7 expected (confidence intervals [CI] not reported) (Chen *et al.*, 1988a).

There was no increase in the incidence of cancer of the testis (odds ratio = 0.91; 95% CI = 0.1–8.6; observed number of cases = 11) in the case–control study described above in which the cases were drawn from a population of approximately 8700 workers involved in production or use of DMF at four plants (Walrath *et al.*, 1989, 1990). Potential exposure to DMF was classified as low or moderate based on job title/work area combinations and monitoring data.

Chen *et al.* (1988a) observed a significant increase in prostate cancer (10 observed vs. 5.1 expected from company rates and 5.2 expected from national rates; $p < 0.10$ for both comparisons) in the 3859 workers exposed either to DMF or to both DMF and ACN. However, when only DMF-exposed workers (2530) were considered, the standardized incidence rate (SIR) (4 observed vs. 2.4 expected from company rates) was not significant. The odds ratio for prostate cancer in the case–control study of the 8700 DMF-exposed workers from four plants was not significantly elevated (1.48; 95% CI = 0.59–3.74; 43 cases) (Walrath *et al.*, 1989, 1990). When analyses were carried out separately for each of the four plants, an increased incidence was observed only at one plant, where the exposure to DMF was lower and the number of cases was fewer than at the other plants. Adjustment for assumed latency period did not alter the odds ratio. There was no relationship with duration of exposure.

Chen *et al.* (1988a) also reported a significant increase in the incidence of cancer of the buccal cavity/pharynx (9 observed vs. 1.6 expected from company rates; $p < 0.10$) in the 2530 DMF-exposed workers (confidence intervals not reported). When combined with data from 1329 workers exposed to both DMF and ACN, the increase (11 observed) was significant when compared with the company rate (3.2 expected, $p < 0.01$), but not when compared with national rates (6.6 expected). There was no relation to either level or duration of exposure. All cases were heavy, long-term smokers. There was no

increase in risk of cancer of the buccal cavity/pharynx in the case–control study of workers at the four plants mentioned above (odds ratio = 0.89; 90% CI = 0.35–2.29, 39 cases) (Walrath *et al.*, 1989, 1990).

2.4.4.2 Effects on the liver

Case reports in workers acutely exposed to DMF confirm that the liver is the target organ, with hepatic effects and associated disorders of the digestive system being reported. Symptoms include abdominal pain, anorexia, incoordination and jaundice, as well as nausea, vomiting and diarrhea; nasal and skin irritation have also been reported (Tolot *et al.*, 1968; Potter, 1973; Chary, 1974; Chivers, 1978; Guirguis, 1981; Paoletti *et al.*, 1982a,b; Riachi *et al.*, 1993; Drouet D'Aubigny *et al.*, 1998; Huang *et al.*, 1998). Changes in both liver function (Weiss, 1971; Potter, 1973; Guirguis, 1981; Paoletti *et al.*, 1982b; Riachi *et al.*, 1993; Drouet D'Aubigny *et al.*, 1998) and morphology (Tolot *et al.*, 1968; Riachi *et al.*, 1993) have also been observed. In one of the few reports where there was some indication of magnitude of exposure, hepatic impairment (marked increases in serum levels of ALT, aspartate aminotransferase [AST], AP and bilirubin, together with fulminant hepatitis and jaundice) was reported in a woman who ingested about 0.6 g DMF/kg-bw (in a formulation containing other ingredients) in a suicide attempt (Nicolas *et al.*, 1990).

Alcohol intolerance, characterized by flushing of the face, dizziness, nausea and tightness of the chest, has been widely reported among DMF-exposed workers (Lyle, 1979; Lyle *et al.*, 1979; Lauwerys *et al.*, 1980; Yonemoto and Suzuki, 1980; Paoletti and Iannaccone, 1982; Paoletti *et al.*, 1982a; Tomasini *et al.*, 1983; Cirla *et al.*, 1984; Redlich *et al.*, 1988, 1990; Wang *et al.*, 1989, 1991; Cai *et al.*, 1992; Fiorito *et al.*, 1997; Wrbitzky, 1999). These symptoms have been associated with exposures to 10 ppm (30 mg/m^3) (Lauwerys *et al.*, 1980; Yonemoto and Suzuki, 1980; Cai *et al.*, 1992; Fiorito *et al.*, 1997); some workers responded to concentrations as low as 1.2 ppm (3.6 mg/m^3) (Wrbitzky, 1999).

Levels of serum hepatic enzymes in populations occupationally exposed to DMF have been determined in several cross-sectional studies. A brief overview of the information on exposure–response derived from these studies is summarized in the following table.

Concentration[1]	Effect on liver enzymes	Exposed population	Confounders	Reference
<10–60 ppm random area sampling	increase	183 workers	some workers were also exposed to solvents	Wang *et al.*, 1989 (abstract), 1991
10–42 ppm area monitoring	increase	13 workers	few details reported	Yang *et al.*, 1994 (abstract)
1–27 ppm	no effect	27 workers		Paoletti and Iannaccone, 1982 (English abstract)
5–20 ppm	increase (significance not reported)	13 workers	exposure to solvents	Tomasini *et al.*, 1983 (English abstract)
3–20 ppm (TWA, 7 ppm) personal sampling	**significant increase**	**100 workers**		**Cirla *et al.*, 1984**
0.3–15.5 ppm (usually <10 ppm) static area sampling	no effect	22 workers		Lauwerys *et al.*, 1980

Concentration[1]	Effect on liver enzymes	Exposed population	Confounders	Reference
1–5 ppm personal and area sampling	no effect	6 workers		Yonemoto and Suzuki, 1980
4–8 ppm (mean, 6 ppm) sampling not specified	**no effect**	**28 workers**		**Catenacci *et al.*, 1984**
0.2–8 ppm area sampling	increase (significance not reported)	26 workers	concomitant exposure to ACN	Major *et al.*, 1998
7 ppm area sampling at different workplaces	**significant increase**	**75 workers**		**Fiorito *et al.*, 1997**
0.1–7 ppm personal sampling	no effect	207 workers	some workers were also exposed to toluene	Cai *et al.*, 1992
up to 2.3 ppm personal sampling	no effect	126 workers		Wrbitzky and Angerer, 1998; Wrbitzky, 1999

[1] 1 ppm = 3 mg/m³.

Increases in serum enzymes were reported in 183 workers exposed to <10–60 ppm (<30–180 mg/m³) DMF (and other solvents) (Wang *et al.*, 1991) and in a smaller group (n = 13) exposed to 10–42 ppm (30–126 mg/m³) (Yang *et al.*, 1994 [abstract]). There were also increases in serum levels of hepatic enzymes in 2 of 13 workers exposed to 5–20 ppm (15–60 mg/m³) DMF (and other solvents) (Tomasini *et al.*, 1983). Cirla *et al.* (1984) reported a significant increase in serum enzymes in 100 workers exposed to a time-weighted average (TWA) of 7 ppm (21 mg/m³) (range 3–20 ppm [9–60 mg/m³]). Major *et al.* (1998) reported an increase in serum enzymes (significance not reported) in 26 workers exposed to 0.2–8 ppm (0.6–24 mg/m³) DMF with concomitant exposure to ACN, and Fiorito *et al.* (1997) observed a significant increase in 12 of 75 workers exposed to 7 ppm (21 mg/m³). There were no increases in serum hepatic enzymes in 22 workers exposed to "<10 ppm" (<30 mg/m³) (Lauwerys *et al.*, 1980), 6 workers exposed to 1–5 ppm (3–15 mg/m³) (Yonemoto and Suzuki, 1980), 28 workers exposed to a mean concentration of 6 ppm (18 mg/m³) (Catenacci *et al.*, 1984), 207 workers exposed to 0.1–7 ppm (0.3–21 mg/m³) (Cai *et al.*, 1992) or 126 workers exposed to up to 2.3 ppm (6.9 mg/m³) (Wrbitzky, 1999).

While there have been considerable variations in the size of study populations, magnitude and duration of exposure, extent of exposure to other substances and adequacy of reporting in these investigations, there is a consistent pattern of increase in serum enzymes in workers with relatively higher exposures in the studies, some of which included individual monitoring. In summary, the results concerning exposure–response are consistent across studies, with increases in serum hepatic enzymes not being observed at concentrations in the range of 1–6 ppm (3–18 mg/m³). At higher levels of exposure (>7 ppm [>21 mg/m³]), increased serum levels of hepatic enzymes have been observed consistently. Women were excluded from analyses because of the small numbers.

Generally, when serum levels of liver transaminases were raised, the AST/ALT ratio was <1, an indication that abnormal function was not due to alcoholic liver disease (Redlich *et al.*, 1988; Fleming *et al.*, 1990).

Three studies were identified (highlighted in the table) for which TWA exposures were presented and which can serve, therefore, as the basis for at least crude estimates of exposure–response. These are described in more detail here.

In an investigation of liver function in 75 male workers in a synthetic leather factory, geometric mean levels of DMF in the air based on area sampling were approximately 20 mg/m^3 (~7 ppm) (range 2–40 mg/m^3) (Fiorito *et al.*, 1997). Skin contact with liquid DMF was also a possibility. The control group consisted of 75 unexposed workers similar in age, sex, social status and residence. All workers underwent a complete physical examination, with liver function tests for serum AST, ALT, gamma-glutamyl transpeptidase (gamma-GT), AP, bile acids, bilirubin, serum cholesterol and triglycerides, and markers for hepatitis A, B and C. Gastrointestinal symptoms (stomach pain, nausea, appetite loss) were reported by 50% of the DMF-exposed workers, and 40% had symptoms such as face flushing, palpitation, headache, dizziness or tremors following alcohol consumption. (Many avoided alcohol as a result.) Mean serum ALT, AST, gamma-GT and AP were significantly higher in the exposed group ($p < 0.001$), and 17/75 (23%) had abnormal liver function, compared with only 4% of controls. Multivariate analyses confirmed that ALT, AST and gamma-GT were significantly correlated with cumulative DMF exposure. The analyses controlled for factors such as body mass index, alcohol intake, serum cholesterol and hepatitis markers.

Catenacci *et al.* (1984) investigated liver function (serum glutamate–oxaloacetate transaminase [SGOT], serum glutamate–pyruvate transaminase [SGPT], gamma-GT and AP) in workers employed for at least 5 years in an acrylic fibre plant. The first group of 28 subjects worked in the spinning department, where DMF exposure (8-hour TWA) ranged from 12 to 25 mg/m^3 (4 to 8 ppm), with a mean of 18 mg/m^3 (6 ppm). The second group consisted of 26 subjects exposed, in the polymer department, to DMF at (8-hour TWA) 1.8–5 mg/m^3 (0.6–1.8 ppm), with a mean of 3 mg/m^3 (1 ppm). A control group consisted of 54 subjects matched for age, smoking/alcohol consumption and history of liver disease, who had never been occupationally exposed to solvents. Mean serum values for SGOT, SGPT, gamma-GT and AP did not differ among the three groups and were within the normal ranges.

Cirla *et al.* (1984) carried out a clinical evaluation of 100 male workers in synthetic polyurethane leather production exposed to a mean TWA concentration (determined by personal sampling) of 22 mg/m^3 (range 8–58 mg/m^3) (mean TWA 7 ppm; range 3–19 ppm). The mean exposure period was 5 years (range 1–15 years). The referent group was 100 workers at the same or similar factories, without exposure to any solvents or toxic metals, matched by sex, age group, alcohol history, smoking habits, coffee intake, socioeconomic status, residence and dietary customs. Clinical evaluation was carried out and a laboratory assessment was performed for blood cell counts and serum AP, AST, ALT and gamma-GT. Serum gamma-GT was abnormally high in 25/100 exposed and only 10/100 referents ($p < 0.01$). Higher prevalences in the exposed group for abnormally high serum levels of AST (9 vs. 3) and ALT (12 vs. 8) were not statistically significant. AP values were normal in all subjects. Several symptoms, including headache, dyspepsia and digestive impairment, characteristic of effects on the liver, were also associated with exposure to DMF.

Histopathological changes in the liver have also been reported in occupationally exposed workers, although quantitative data on levels of exposure are not well documented. Tomasini *et al.* (1983) reported hepatic pain and palpable liver in 4 of 13 workers exposed to 5–20 ppm (15–60 mg/m^3) DMF (and other solvents) for periods ranging from a few weeks to 4 years. Redlich *et al.* (1990) carried out biopsies of liver from workers heavily exposed to DMF (and other solvents; quantitative data not reported). Workers exposed for less than 3 months had hepatocellular necrosis, enlarged Kupffer cells, microvesicular steatosis, complex lysosomes and pleomorphic mitochondria. The liver of workers exposed for longer terms (14–120 months) had fatty changes with occasional lipogranuloma.

2.4.4.3 Cardiac effects

Excess mortality from ischemic heart disease in DMF-exposed workers in a U.S. ACN fibre plant was observed in a historical cohort study (Chen *et al.*, 1988b). Between 1950 and 1982, there were 62 deaths due to ischemic heart disease (40.3 expected from company rates; $p < 0.01$). The increase was not significant in comparison with the state (South Carolina) rates. A similar observation was made for a second group of 1329 employees at the plant who were potentially exposed to both DMF and ACN (65 deaths observed, 48.3 expected from company rates; $p < 0.05$). However, the rate was not significantly higher than either state or national rates. Lifestyle factors were suggested to be more likely causes than exposure to DMF (Chen *et al.*, 1988b).

No convincing evidence of adverse effects on cardiac function was seen in a limited study in which electrocardiographic (ECG) monitoring was carried out on workers at a small synthetic leather plant where DMF was used. Monitoring of eight workers over a work shift revealed possible mild effects (isolated ventricular premature beats after 2 hours of work, without "pathological alteration" of the ECG) in one worker (Taccola *et al.*, 1981). In a brief report, ECG changes in workers exposed to DMF were reported (<3 ppm [<9 mg/m^3], with peaks up to 1500 ppm [4500 mg/m^3], plus skin exposure), but little detail was provided (Kang-De and Hui-Lan, 1981).

Cardiac disturbances, including tachycardia and palpitations, have occasionally been observed in cross-sectional studies of DMF-exposed workers (Lyle, 1979; Lyle *et al.*, 1979; Kang-De and Hui-Lan, 1981; Cirla *et al.*, 1984; Fiorito *et al.*, 1997). Sometimes, the palpitations followed alcohol ingestion (Lyle, 1979; Lyle *et al.*, 1979; Fiorito *et al.*, 1997).

2.4.4.4 Genotoxicity

Seven studies were identified in which the genotoxicity of DMF in humans has been examined. Four of these studies were critically reviewed by IARC (1999) and were described therein as follows.

Berger *et al.* (1985) reported that the prevalence of CAs was higher in the blood lymphocytes of 20 workers exposed to DMF, NMF and dimethylamine than in 18 unexposed workers at the same factory (1.4% vs. 0.4%; statistical significance not provided). The mean concentrations 1 year prior to blood sampling were 12.3 mg/m^3 for DMF, 5.3 mg/m^3 for NMF and 0.63 mg/m^3 for dimethylamine. However, the control group had an unusually low level of chromosome breaks. The IARC Working Group noted that the possible effect of smoking was not addressed.

A higher incidence of CAs was observed in the lymphocytes of about 40 workers exposed to DMF than in an unspecified control group (2.74–3.82% vs. 1.10–1.61%; $p < 0.05$). The range of exposure to DMF was 150–180 mg/m^3. Workers were also exposed to trace amounts of methyl ethyl ketone, butyl acetate, toluene, cyclohexanone and xylene. After technological improvements designed to reduce DMF exposure levels (range 35–50 mg/m^3), the frequency of aberrant cells decreased to 1.49–1.59% (Koudela and Spazier, 1981).

Although Sram *et al.* (1985) reported in an abstract that there was no evidence of increased frequency of CA in peripheral lymphocytes in workers exposed to DMF, no details were provided.

Seiji *et al.* (1992) reported that the mean SCE rate was higher in the blood cells of 22 women exposed to three concentrations of DMF (0.3–5.8 ppm [0.9–17.4 mg/m^3]) in a leather production factory than in 22 unexposed controls from the same factory, matched by sex, age and residence. None of the women smoked tobacco or drank alcohol. The incidence of SCEs was significantly increased in a dose-related manner in the mid- and high-exposure groups.

Based on review of these studies, IARC (1999) concluded that "The positive data for cytogenetic damage in humans occupationally exposed to it are not very convincing."

Three relevant reports, including one for which only an abstract was identified in which few details were provided (Haber *et al.*, 1990), were identified in addition to those reviewed by IARC (1999). The two investigations for which reporting was adequate are described here.

Major *et al.* (1998) reported that for workers with 3–10 years of occupational exposure to undefined levels of DMF and/or ACN, the prevalence of peripheral lymphocytes with CAs was increased compared with unexposed controls (see below). After a further 7 months' exposure (to DMF at 0.2–8 ppm [0.6–24 mg/m^3] and ACN at 0–17.6 mg/m^3), the incidence in the exposed group increased to 5.1% but did not increase further up to 20 months. The incidence of SCEs was also higher than control values at the start of the 20-month study and remained higher at 7 and 20 months. The UDS level was similar to that in controls when the study started but had increased in the exposed group by month 7. In addition to concomitant exposure to ACN, current smoking was also a confounding factor, with CA and SCE yields being significantly higher in exposed smokers than in exposed non-smokers. Nevertheless, CA yields at 7 months were significantly higher in exposed non-smokers than in control non-smokers and in exposed smokers than in control smokers.

Cheng *et al.* (1999) measured SCE frequency in peripheral lymphocytes of workers at a resin synthesis plant. Nine workers had low exposure (median 5.2 ppm [15.6 mg/m^3]; range 0.9–5.3 ppm [2.7–15.9 mg/m^3]) and 20 workers had high exposure (median 24.8 ppm [74.4 mg/m^3]; range 11.4–83.3 ppm [34.2–249.9 mg/m^3]). There were no differences between the two groups; there was no additional control population.

Results of studies on genotoxicity conducted since the IARC evaluation have not contributed materially to the database that was considered by IARC (1999) not to provide convincing evidence. Certainly, the results, when taken as a whole, are inconsistent and not readily explained by variations in exposure.

3.0 ASSESSMENT OF "TOXIC" UNDER CEPA 1999

3.1 CEPA 1999 64(a): Environment

The environmental risk assessment of a PSL substance is based on the procedures outlined in Environment Canada (1997a). Analysis of exposure pathways and subsequent identification of sensitive receptors are used to select environmental assessment endpoints (e.g., adverse reproductive effects on sensitive fish species in a community). For each endpoint, a conservative Estimated Exposure Value (EEV) is selected and an Estimated No-Effects Value (ENEV) is determined by dividing a Critical Toxicity Value (CTV) by an application factor. A hyperconservative or conservative quotient (EEV/ENEV) is calculated for each of the assessment endpoints in order to determine whether there is potential ecological risk in Canada. If these quotients are less than one, it can be concluded that the substance poses no significant risk to the environment, and the risk assessment is completed. If, however, the quotient is greater than one for a particular assessment endpoint, then the risk assessment for that endpoint proceeds to an analysis where more realistic assumptions are used and the probability and magnitude of effects are considered. This latter approach involves a more thorough consideration of sources of variability and uncertainty in the risk analysis.

3.1.1 Terrestrial assessment endpoints

Since most DMF appears to be released to air in Canada, and based on the fate of DMF in the ambient environment, biota are expected to be exposed to DMF primarily in air; little exposure to surface water, soil or benthic organisms is expected. Based on this, and because of the low toxicity of DMF to a wide range of aquatic and soil organisms, it is unlikely that organisms will be exposed to harmful levels of DMF in Canadian surface waters, soils or groundwater. Therefore, the focus of the environmental risk characterization is on terrestrial organisms exposed directly to DMF in ambient air.

Terrestrial plants can be exposed to DMF by direct contact with the atmosphere, but also conceivably by diffusion from raindrops deposited on leaves. No data are available on the toxicity of DMF to terrestrial vascular plants. Seeds, soil fungi and aquatic angiosperm macrophytes can be used as indicators of the potential sensitivities of trees, shrubs and other plants. The most sensitive of these organisms appears to be the soil fungus, *Sclerotinia homeocarpa*, with an EC_{50} of 4840 mg/L for growth inhibition (Stratton, 1985). In view of the generally high effect concentrations relative to other species, it is unlikely that terrestrial plants are particularly sensitive to DMF exposure.

As most DMF is reportedly released to air, and as bioaccumulation is not expected, effects on wildlife will occur mainly through direct exposure by inhalation in the vicinity of the point source. Based on the available information, the home range of common small-sized eastern Canadian mammals (e.g., voles, squirrels, mice) is generally much less than 1 km^2 (Banfield, 1974; Burt and Grossenheider, 1976; Forsyth, 1985; U.S. EPA, 1999b). By contrast, the home range of the raccoon, a common suburban visitor, is quite variable in size, reportedly ranging from a few square kilometres to thousands of square kilometres (Burt and Grossenheider, 1976; U.S. EPA, 1999b). Therefore, small-sized mammals may be exposed, over long periods of time, to the highest concentrations of DMF within a few kilometres of the site, while the more mobile larger mammals are probably exposed over time to lower average levels of DMF.

No information has been found on the effects of DMF on wildlife. Experimental animals used in laboratory studies are used as surrogates for small and medium-sized mammals exposed to DMF through inhalation.

3.1.2 Environmental risk characterization

3.1.2.1 Terrestrial organisms

With a reported annual loading of less than 20 tonnes and generally less than 1 tonne at any location in Canada, continuous releases of consistent magnitude likely result in long-term exposure to low concentrations of DMF near point sources. Because of the absence of empirical data on concentrations of DMF in air in Canada, an EEV was calculated based on release data for the largest Canadian emitter, making several conservative assumptions.

The largest annual release reported at one location can be expressed on a daily basis (12.7 tonnes/year = 0.0348 tonnes/day or 3.48×10^7 mg/day). As a conservative estimate, it will be assumed that daily releases of DMF are contained within a cylinder having a radius of 1 km centred on the point source. Dispersion within 1 km is likely a conservative assumption, for a number of reasons. First, the greatest reported emissions are occurring in a mixed industrial and agricultural area (Environment Canada, 1999). The site is paved with asphalt, and, as such, wild plants and mammals will not likely be found in the immediate vicinity of the source. Finally, although the specific dispersal behaviour of DMF has not been documented near the source, results of dispersion modelling indicate that concentrations of other contaminants released to air elsewhere tend to decrease rapidly within a few kilometres of industrial point sources (e.g., Davis, 1997; Thé, 1998).

Upward movement of organic compounds released to the atmosphere generally does not exceed 100 m at night but may exceed 1000 m during the day (Bunce, 1998a). The more conservative value of 100 m will be used as a ceiling for estimating the exposure concentrations.

This provides a dispersal volume of 3.14×10^8 m^3 in the form of a cylinder 100 m in height and 1 km in radius. With a daily release of 3.48×10^7 mg/day, the daily increase in the concentration of DMF in air is estimated at 0.11 mg/m^3 and will be used as a conservative EEV. Reaction with hydroxyl radicals will tend to reduce the concentrations of DMF in the daytime. Since the degradation half-life of DMF could be a week or more, continuous daily inputs would lead to buildup of DMF within the cylinder in the absence of any other loss process. However, fugacity-based modelling suggests that advection processes, i.e., rain and wind, are the major factors in determining concentrations in the atmosphere. Even under essentially stagnant conditions, with a wind speed of 1 km/hour, the rate of advection of DMF out of the cylinder is so fast that the steady-state concentration would be 0.01 mg/m^3 or less. At a typical average wind speed of 10 km/hour, the concentration of DMF in the cylinder would be reduced by a factor of approximately 100. The EEV of 0.11 mg/m^3 is generally higher than or comparable to measurements made in other countries (Section 2.3.2).

The chronic inhalation (18 months) LOEC of 75 mg/m^3 (25 ppm) measured for mice (Malley *et al.*, 1994) is used as the CTV for exposure of small mammals. This value was selected from a large data set composed of acute and chronic studies conducted on a number of laboratory species. Although no direct effects related to survival were observed at the exposure concentrations used in this study (up to 1200 mg/m^3 [400 ppm]), nor were any hematological changes or effects on the estrous cycle observed, there was an increased incidence of hepatocellular hypertrophy, hepatic single-cell necrosis and hepatic Kupffer cell hyperplasia/pigment accumulation at 75 mg/m^3 (Malley *et al.*, 1994). Such effects may not directly manifest themselves

as population-level effects in wildlife species; therefore, the ENEV is derived by dividing the CTV by a reduced application factor of 5. This factor also accounts for the extrapolation from a lowest-effect level to a no-effect level, as well as the uncertainty surrounding the extrapolation from laboratory to field conditions and interspecies and intraspecies variability in sensitivity. As a result, the ENEV is 15 mg/m^3. The risk quotient is calculated by dividing the EEV (0.11 mg/m^3) by the ENEV:

$$\text{Quotient} = \frac{\text{EEV}}{\text{ENEV}}$$

$$= \frac{0.11 \text{ mg/m}^3}{15 \text{ mg/m}^3}$$

$$= 0.007$$

Since this conservative quotient is less than 1, it is unlikely that DMF causes adverse effects on terrestrial organisms in Canada.

3.1.2.2 Discussion of uncertainty

There are a number of potential sources of uncertainty in this environmental risk assessment. The calculated Henry's law constant is uncertain, as it is based on a water solubility that is infinite. Sensitivity analysis suggests that the fugacity-based partitioning estimates can be sensitive to the value used as the Henry's law constant (Bobra, 1999).

Because the half-life in air (~8 days) is only estimated, there is the possibility that the value is underestimated. A longer half-life would tend to increase, to some extent, the GWP of DMF. Sensitivity analysis on the fugacity-based results indicates that percent partitioning estimates are not sensitive to this parameter, but estimated concentrations are affected (Bobra, 1999).

Ambient levels near Canadian sources are not available. The EEV was therefore estimated based on available information on releases. This calculated EEV is, however, generally consistent with the highest concentrations measured in other countries. It is unlikely that there are concentrations of DMF in Canada that are higher than those calculated and used in this assessment. For air, reported releases at the selected location by far exceed reported releases to air at any other location and, as such, likely constitute a worst case. For water, concentrations are expected to be low because of the limited releases to this medium identified and the limited partitioning of DMF from air into water. Small spills and leakage could increase levels of DMF in soil and groundwater; however, the available information suggests that such releases would be small and infrequent.

Regarding effects of DMF on terrestrial organisms, although no toxicity data were identified for vascular plants, data on effects of DMF on seeds and aquatic macrophytes suggest that terrestrial vegetation is not particularly sensitive to DMF. Additional evidence of effects on terrestrial plants would strengthen the conclusion that DMF is not expected to damage gymnosperms, angiosperms or other vascular plants.

There is uncertainty concerning the extrapolation from a lowest-effect level to a no-effect level and from laboratory mammals to potential effects on wildlife populations. To account for these uncertainties, an application factor was used in the environmental risk analysis to derive an ENEV.

Despite some data gaps regarding the environmental effects of and exposure to DMF, the data available at this time are considered adequate for making a conclusion on the environmental risk of DMF in Canada.

3.2 CEPA 1999 64(b): Environment upon which life depends

DMF does not deplete stratospheric ozone, and its potential for contributing to climate change is negligible. Given its low reactivity in air and low release rate into air, DMF is not likely to contribute to the photochemical formation of ground-level ozone.

3.3 CEPA 1999 64(c): Human health

3.3.1 Estimated population exposure

Identified data on concentrations of DMF in environmental media in Canada are insufficient to allow estimates of population exposure to be developed. Concentrations in food in Canada or elsewhere were not identified; for water, either quantitative data on concentrations are unreliable (OMEE, 1996) or DMF has not been detected, using analytical methodology with poor sensitivity (Conor Pacific Environmental, 1998).

Non-pesticidal use of DMF in Canada is small and restricted primarily to industrial applications. Most DMF released into the environment in Canada during such use is emitted to air (Section 2.2.2.2). Most DMF remains in the medium of release prior to degradation (Section 2.3.1.4). Therefore, the greatest potential for exposure of the general population to DMF from non-pesticidal sources is in air in the vicinity of industrial point sources. Based on dispersion modelling of releases from the highest emitter over a 1-km radius, 100 m in height, the estimated ambient concentration is 0.11 mg/m^3 (110 µg/m^3) (Section 3.1.2.1). Although this value is comparable to levels measured under similar conditions in other countries, it is based on very conservative assumptions; taking into account more likely conditions, including some loss due to advection, estimated concentrations would be 10- to 100-fold less (i.e., 11 or 1.1 µg/m^3).

Based on lack of detection in the multimedia study, levels of DMF in indoor air of 50 homes were less than 3.4 µg/m^3 (Conor Pacific Environmental, 1998).

3.3.2 Hazard characterization

3.3.2.1 Effects on humans

Consistent with the results of studies in experimental animals, available data from case reports and cross-sectional studies in occupationally exposed populations indicate that the liver is the target organ for the toxicity of DMF in humans. The profile of effects is consistent with that observed in experimental animals, with gastrointestinal disturbance, alcohol intolerance, increases in serum hepatic enzymes (AST, ALT, gamma-GT and AP) and histopathological effects (hepatocellular necrosis, enlarged Kupffer cells, microvesicular steatosis, complex lysosomes, pleomorphic mitochondria and fatty changes with occasional lipogranuloma) being observed.

Based on the limited data available, there is no convincing, consistent evidence of increases in tumours at any site associated with exposure to DMF in the occupational environment. Case reports of testicular cancers have not been confirmed in a cohort and case–control study. There have been no consistent increases in tumours at other sites associated with exposure to DMF.

There is also little consistent, convincing evidence of genotoxicity in populations occupationally exposed to DMF, with results of available studies of exposed workers (DMF and other compounds) being mixed. The pattern of observations is not consistent with variations in exposure across studies; however, in view of the positive dose–response relationship observed in the one study in which it was investigated, this area may be worthy of additional work, although available data on genotoxicity in experimental systems are overwhelmingly negative.

3.3.2.2 Effects on experimental animals

DMF has low acute toxicity and is slightly to moderately irritating to the eyes and skin. In acute and repeated-dose toxicity studies, it has been consistently hepatotoxic, inducing effects on the liver at lowest concentrations or doses. The profile of effects includes alterations in hepatic enzymes and increases in liver weight, progressive degenerative histopathological changes and eventually cell death and increases in serum hepatic enzymes. Species variations in sensitivity to these effects have been observed, with the order of sensitivity being mice > rats > monkeys.

Although the database for carcinogenicity is limited to two adequately conducted bioassays in rats and mice, there have been no increases in the incidence of tumours following chronic inhalation exposure to DMF. The weight of evidence for genotoxicity is overwhelmingly negative, based on extensive investigation in *in vitro* assays, particularly for gene mutation, and a more limited database *in vivo*.

DMF has induced adverse reproductive effects only at concentrations considerably greater than those associated with adverse effects on the liver. In developmental studies, in adequately conducted and reported primarily recent studies, fetotoxic and teratogenic effects have been consistently observed only at maternally toxic concentrations or doses.

Available data are inadequate as a basis for assessment of the neurological or immunological effects of DMF.

3.3.3 Dose–response analysis

In both humans and experimental animals exposed to DMF, the target organ has been the liver, consistent with local action of a reactive intermediate in the tissue in which it is primarily metabolized. Available data indicate that there are considerable variations between experimental animals and humans in the proportion of DMF metabolized by the putatively toxic pathway, with the resulting implication that humans may be more sensitive to the effects of DMF. Also, since there are data available to serve as a basis for at least crude characterization of exposure–response for parameters associated with hepatic toxicity in workers, the Tolerable Concentration (TC) is based on data in humans. Analyses of dose–response for hepatic effects in the studies in experimental animals are presented for comparison. Since exposure in the general environment is likely to be primarily through air, emphasis in this section is on the generally more extensive database on toxicity by the inhalation route.

3.3.3.1 Humans

Effects on the liver observed at lowest concentration in cross-sectional studies in occupationally exposed populations for which there is some information on exposure–response are increases in serum hepatic enzymes. The results concerning exposure–response are consistent across studies, with increases in serum hepatic enzymes not being observed at concentrations in the range of 1–6 ppm (3–18 mg/m^3). At higher levels of exposure (>7 ppm [>21 mg/m^3]), increased serum levels of hepatic enzymes have been observed consistently. The study in the largest group of workers that included individual monitoring of exposure is that of Cirla *et al.* (1984), in which there were significant increases in serum gamma-GT in 100 workers exposed to 7 ppm (21 mg/m^3) (TWA, determined by personal sampling), compared with 100 controls matched for age, sex, alcohol consumption, smoking habits, coffee intake, socioeconomic status, residence and dietary habits (SGOT and SGPT were not increased). Study subjects were selected to minimize large variations in exposure; those with histories of possible accidental exposures were also excluded. When subjects who had not modified their alcohol consumption upon working with DMF were considered, the effect was still evident. The workers were also exposed to small (but

unspecified) quantities of toluene, methyl ethyl ketone, ethyl acetate isopropyl alcohol and isobutyl alcohol.

Results of this study are consistent with those of a carefully conducted study by Fiorito *et al.* (1997), in which serum ALT, AST, gamma-GT and AP were significantly increased in 12 of 75 workers exposed to 7 ppm (21 mg/m^3) DMF (geometric mean), compared with 75 controls matched by age, sex, residence and social status. Confounding by alcohol consumption and pre-existing liver disease was minimized through selection criteria for study subjects. The impact of obesity, hepatitis markers and alcohol consumption was considered but did not explain the observed effects. Analysis of paired enzymes was also conducted. It was reported that the study subjects worked in a factory that produces synthetic leather using polyurethane resin, pigments and large amounts of DMF (about 15 tonnes/day). Levels of DMF were based on 8-hour area sampling in various working locations.

Catenacci *et al.* (1984) did not observe differences between serum enzyme levels of SGOT, SGPT and gamma-GT in 28 workers employed for more than 5 years and exposed to a mean TWA of 6 ppm (18 mg/m^3) DMF or 26 subjects employed for more than 5 years and exposed to a mean TWA of 1 ppm (3 mg/m^3) and 54 controls matched for age, smoking status, alcohol consumption and history of liver disease. Few details were presented in the published account of this study. It was noted that these workers were employed in an acrylic fibre plant; no mention was made of exposure to other solvents. The data on which the estimated TWA exposures were based were not reported. In view of the small number of subjects exposed to the mean TWA of 6 ppm (18 mg/m^3) DMF (n = 28), negative results reported therein may be a function of lack of power of the study to detect a meaningful effect and are not, therefore, necessarily inconsistent with the results of Cirla *et al.* (1984) and Fiorito *et al.* (1997).

Based on the Lowest-Observed-Adverse-Effect Level (LOAEL) of 7 ppm (21 mg/m^3), a TC has been derived as follows:

$$TC = \frac{7 \text{ ppm } (21 \text{ mg/m}^3) \times 8/24 \times 5/7}{50}$$

$$= 0.03 \text{ ppm } (0.1 \text{ mg/m}^3)$$

where:

- 7 ppm (21 mg/m^3) is the LOAEL for increases in serum hepatic enzymes in workers exposed primarily to DMF reported by Cirla *et al.* (1984) and Fiorito *et al.* (1997); it should be noted that the observed small increases in a few serum hepatic enzymes are considered to be only minimally adverse, with associated hepatic damage likely being fully reversible upon cessation of exposure.
- 8/24 and 5/7 are the factors to convert exposure during 8 hours per day and 5 days per work week, respectively, to continuous exposure.
- 50 is the uncertainty factor (×10 for intraspecies [interindividual][2] variation, including sensitive subgroups; ×5 to account primarily for less than lifetime exposure; although the TC is based on a LOAEL, observed effects are considered to be only minimally adverse).

[2] Available quantitative data are insufficient to replace default values for the component of this uncertainty factor with data-derived values (Health Canada, 1994).

3.3.3.2 Experimental animals

In subchronic inhalation assays in F344 rats, there was an increase in relative liver weight in females and increased cholesterol in both sexes at 50 ppm (150 mg/m³) (LOEC), with no clear dose–response (NTP, 1992a), progressive histopathological hepatic changes in both sexes at 400 and 800 ppm (1200 and 2400 mg/m³) (Craig *et al.*, 1984) and hepatocellular necrosis in both sexes at 400 ppm (1200 mg/m³) (NTP, 1992a). B6C3F1 mice had hepatocellular hypertrophy at 50 ppm (150 mg/m³) (LOEC), in addition to significantly increased relative liver weight in both sexes without clear dose–response (NTP, 1992a) and hepatic cytomegaly at 150 ppm (450 mg/m³) and higher (Craig *et al.*, 1984). No signs of toxicity were observed in monkeys exposed to up to 500 ppm (1500 mg/m³) (Hurtt *et al.*, 1992).

In a chronic inhalation bioassay in Crl:CD BR rats, at 100 ppm (300 mg/m³), there were significant increases in centrilobular hepatocellular hypertrophy (both sexes), hepatic accumulation of lipofuscin/hemosiderin (both sexes) and hepatic single-cell necrosis (females only). In mice [Crl:CD 1 (ICR)BR], at 25 ppm (75 mg/m³), there was centrilobular hepatocellular hypertrophy (males), hepatic single-cell necrosis (males and females) and hepatic Kupffer cell hyperplasia/pigment accumulation (males) (Malley *et al.*, 1994).

Data on dose–response following ingestion are limited to subchronic studies. At 250 mg/kg-bw per day, liver cell enlargement was reported in Crl:CD rats; at 50 mg/kg-bw per day, relative liver weight was significantly increased in males (Kennedy and Sherman, 1986). In Wistar rats, relative liver weight was significantly increased at 69 mg/kg-bw per day, but no histopathological lesions were observed at doses up to 235 mg/kg-bw per day (Becci *et al.*, 1983). In CD-1 mice, only mild histopathological changes were observed in the liver at 246 mg/kg-bw per day; at 96 mg/kg-bw per day, relative liver weight was significantly increased in females. No adverse effects were observed in beagle dogs administered up to 34.8 mg/kg-bw per day in the diet for 13 weeks.

It should be noted that the lowest concentration (50 ppm [150 mg/m³]) at which effects were observed in the liver of rats (NTP, 1992a) in an inhalation assay is equivalent to an intake of 46.5 mg/kg-bw per day in rats,[3] which is consistent with the effect levels in Crl:CD rats (Kennedy and Sherman, 1986) and Wistar rats (Becci *et al.*, 1983) following dietary exposure. The lowest concentration (50 ppm [150 mg/m³]) to which mice were exposed in NTP (1992a) is equivalent to an intake of 200 mg/kg-bw per day,[4] which is consistent with the effect levels in the dietary assay in mice reported by Becci *et al.* (1983).

Reported incidence, benchmark concentrations at the 5% level (BMC_{05}) and associated p-values and goodness of fit statistics for effects on the liver for relevant endpoints for which fits were acceptable in the most robust subchronic and chronic studies for inhalation and ingestion, respectively, are presented in Tables 3 and 4.

For the discrete endpoints, the BMC_{05} is defined as the concentration of chemical that is estimated to cause a 5% increase in incidence over the background response rate. It is calculated by first fitting the following model to the dose–response data (Howe, 1995):

[3] 1 mg/m³ = 0.31 mg/kg-bw per day in rats (Health Canada, 1994).

[4] 1 mg/m³ = 1.33 mg/kg-bw per day in mice (Health Canada, 1994).

TABLE 3 Effect levels and benchmark concentrations for DMF, inhalation exposure

Study (reference)	Effect level	Data for calculating benchmark concentration		Benchmark concentration[1]		
		Concentration	Response	Parameter estimates		Goodness of fit
Subchronic assays						
B6C3F1 mice 10 males and 10 females per group 0, 50, 100, 200, 400, 800 ppm, 6 hours/day, 5 days/week, for 13 weeks (NTP, 1992a)	LOEC = 50 ppm, based upon increased relative liver weight in both sexes and hepatocellular hypertrophy in males	control 50 ppm 100 ppm 200 ppm 400 ppm 800 ppm	Male, incidence (severity) of centrilobular hepatocellular hypertrophy: 0/10 4/10 (1.8) 9/10 (1.3) 10/10 (2.0) 10/10 (2.0) 10/10 (2.0)	BMC_{05} = 8.5 ppm excluding 400 and 800 ppm groups	95% LCL_{05} = 2.5 ppm excluding 400 and 800 ppm groups	Chi-square (1) = 0.004 p-value = 0.99
				Adjusted BMC_{05} = 1.51 ppm	Adjusted 95% LCL_{05} = 0.44 ppm	
		control 50 ppm 100 ppm 200 ppm 400 ppm 800 ppm	Female, incidence (severity) of centrilobular hepatocellular hypertrophy: 0/10 0/10 10/10 (1.3) 10/10 (1.9) 10/10 (2.0) 10/10 (2.0)	BMC_{05} = 17.9 ppm excluding 200, 400 and 800 ppm groups	95% LCL_{05} = 8.1 ppm excluding 200, 400 and 800 ppm groups	Chi-square (1) = 7.5 p-value = 0.01
				Adjusted BMC_{05} = 3.19 ppm excluding 200, 400 and 800 ppm groups	Adjusted 95% LCL_{05} = 1.45 ppm excluding 200, 400 and 800 ppm groups	

Table 3 (continued)

Study (reference)	Effect level	Data for calculating benchmark concentration		Benchmark concentration[1]		
		Concentration	Response	Parameter estimates		Goodness of fit
Chronic toxicity/carcinogenicity assays						
Rat, Crl:CD BR 87 males and 87 females per group 0, 25, 100, 400 ppm, 6 hours/day, 5 days/week, for 2 years (Malley *et al.*, 1994)	LOEC = 100 ppm, based upon a significant increase in centrilobular hepatocellular hypertrophy (both sexes), significant increase in hepatic accumulation of lipofuscin/hemosiderin (both sexes) and hepatic single-cell necrosis (females only) NOEC = 25 ppm	control (n = 60) 25 ppm (n = 59) 100 ppm (n = 59) 400 ppm (n = 62)	females, hepatic accumulation of lipofuscin/hemosiderin: 8% 7% 22% ($p < 0.05$) 61% ($p < 0.05$)	BMC_{05} = 37.0 ppm Adjusted BMC_{05} = 6.61 ppm	95% LCL_{05} = 19.8 ppm Adjusted 95% LCL_{05} = 3.54 ppm	Chi-square (1) = 1.01 p-value = 0.31
		control (n = 57) 25 ppm (n = 59) 100 ppm (n = 58) 400 ppm (n = 60)	males, hepatic accumulation of lipofuscin/hemosiderin: 4% 4% 17% ($p < 0.05$) 58% ($P < 0.05$)	BMC_{05} = 41.4 ppm Adjusted BMC_{05} = 7.39 ppm	95% LCL_{05} = 21.9 ppm Adjusted 95% LCL_{05} = 3.91 ppm	Chi-square (1) = 0.84 p-value = 0.36
		control (n = 17) 25 ppm (n = 19) 100 ppm (n = 21) 400 ppm (n = 26)	males, relative liver weight: 2.87 2.81 3.28 3.58 ($p < 0.05$)	BMC_{05} = 44.5 ppm Adjusted BMC_{05} = 7.95 ppm	95% LCL_{05} = 23.7 ppm Adjusted: 95% LCL_{05} = 4.23 ppm	F(1,79) = 2.09 p-value = 0.15
		control (n = 57) 25 ppm (n = 59) 100 ppm (n = 58) 400 ppm (n = 60)	males, hepatic foci of alterations (clear cell): 11% 8% 22% ($p < 0.05$) 35% ($p < 0.05$)	BMC_{05} = 5.7 ppm Adjusted BMC_{05} = 10.3 ppm	95% LCL_{05} = 37.8 ppm Adjusted 95% LCL_{05} = 6.75 ppm	Chi-square (2) = 1.71 p-value = 0.42
		control (n = 60) 25 ppm (n = 59) 100 ppm (n = 59) 400 ppm (n = 62)	females, hepatic foci of alterations (clear cell): 5% 5% 14% 24% ($p < 0.05$)	BMC_{05} = 84.3 ppm Adjusted BMC_{05} = 15.1 ppm	95% LCL_{05} = 53.4 ppm Adjusted 95% LCL_{05} = 9.54 ppm	Chi-square (2) = 0.77 p-value = 0.68

TABLE 3 (continued)

Study (reference)	Effect level	Data for calculating benchmark concentration		Benchmark concentration[1]		
		Concentration	Response	Parameter estimates		Goodness of fit
Mice, Crl:CD 1 (ICR)BR 78 males and 78 females per group 0, 25, 100, 400 ppm, 6 hours/day, 5 days/week, for 18 months (Malley *et al.*, 1994)	LOEC = 25 ppm, based upon centrilobular hepatocellular hypertrophy (males), hepatic single-cell necrosis (males and females) and hepatic Kupffer cell hyperplasia/pigment accumulation (males)	control (n = 22) 25 ppm (n = 14) 100 ppm (n = 12) 400 ppm (n = 23)	females, relative liver weight: 3.12 3.43 3.33 3.86 ($p < 0.05$)	BMC_{05} = 101.6 ppm	95% LCL_{05} = 46.2 ppm	F(1,67) = 1.12 p-value = 0.29
				Adjusted BMC_{05} = 18.1 ppm	Adjusted 95% LCL_{05} = 8.25 ppm	
		control (n = 57) 25 ppm (n = 59) 100 ppm (n = 58) 400 ppm (n = 60)	males, centrilobular hepatocellular hypertrophy: 0 0 5% ($p < 0.05$) 30% ($p < 0.05$)	BMC_{05} = 118.7 ppm	95% LCL_{05} = 56.4 ppm	Chi-square (1) = 0.65 p-value = 0.42
				Adjusted BMC_{05} = 21.2 ppm	Adjusted 95% LCL_{05} = 10.1 ppm	
		control (n = 60) 25 ppm (n = 59) 100 ppm (n = 59) 400 ppm (n = 62)	females, centrilobular hepatocellular hypertrophy: 0 0 3% ($p < 0.05$) 40% ($p < 0.05$)	BMC_{05} = 126.7 ppm	95% LCL_{05} = 77.7 ppm	Chi-square (1) = 0.13 p-value = 0.72
				Adjusted BMC_{05} = 22.6 ppm	Adjusted 95% LCL_{05} = 13.9 ppm	
		control (n = 60) 25 ppm (n = 59) 100 ppm (n = 59) 400 ppm (n = 62)	females, hepatic single cell necrosis: 0 0 5% ($p < 0.05$) 18% ($p < 0.05$)	BMC_{05} = 126.9 ppm	95% LCL_{05} = 72.9 ppm	Chi-square (1) = 0.78 p-value = 0.38
				Adjusted BMC_{05} = 22.7 ppm	Adjusted 95% LCL_{05} = 13.0 ppm	
		control (n = 61) 25 ppm (n = 63) 100 ppm (n = 61) 400 ppm (n = 63)	females, hepatic single-cell necrosis: 29% 44% ($p < 0.05$) 70% ($p < 0.05$) 76% ($p < 0.05$)	BMC_{05} = 16.8 ppm BMC_{05} = 5.9 ppm excluding 400 ppm group	95% LCL_{05} = 11.9 ppm 95% LCL_{05} = 4.1 ppm excluding 400 ppm group	Chi-square (2) = 9.7 p-value = 0.00 (Chi-square (1) = 0.02 p-value = 0.88)
				Adjusted BMC_{05} = 3.00 ppm BMC_{05} = 1.05 ppm excluding 400 ppm group	Adjusted 95% LCL_{05} = 2.13 ppm 95% LCL_{05} = 0.73 ppm excluding 400 ppm group	

Table 3 (continued)

Study (reference)	Effect level	Data for calculating benchmark concentration		Benchmark concentration[1]		
		Concentration	Response	Parameter estimates		Goodness of fit
		control (n = 60) 25 ppm (n = 62) 100 ppm (n = 60) 400 ppm (n = 59)	males, hepatic single-cell necrosis: 24% 59% (p < 0.05) 68% (p < 0.05) 87% (p < 0.05)	BMC_{05} = 10.8 ppm Adjusted BMC_{05} = 1.93 ppm	95% LCL_{05} = 7.8 ppm Adjusted 95% LCL_{05} = 1.39 ppm	Chi-square (2) = 13.4 p-value = 0.00
		control (n = 60) 25 ppm (n = 62) 100 ppm (n = 60) 400 ppm (n = 59)	males, hepatic Kupffer cell hyperplasia/ pigment accumulation: 22% 52% (p < 0.05) 60% (p < 0.05) 86% (p < 0.05)	BMC_{05} = 11.1 ppm Adjusted BMC_{05} = 1.98 ppm	95% LCL_{05} = 8.2 ppm Adjusted 95% LCL_{05} = 1.46 ppm	Chi-square (2) = 7.5 p-value = 0.02
		control (n = 61) 25 ppm (n = 63) 100 ppm (n = 61) 400 ppm (n = 63)	females, hepatic Kupffer cell hyperplasia/pigment accumulation: 51% 57% 71% (p < 0.05) 89% (p < 0.05)	BMC_{05} = 13.4 ppm Adjusted BMC_{05} = 2.39 ppm	95% LCL_{05} = 9.3 ppm Adjusted 95% LCL_{05} = 1.66 ppm	Chi-square (2) = 0.35 p-value = 0.84
		control (n = 60) 25 ppm (n = 62) 100 ppm (n = 60) 400 ppm (n = 59)	males, centrilobular hepatocellular hypertrophy: 0 8% (p < 0.05) 41% (p < 0.05) 52% (p < 0.05)	BMC_{05} = 18.9 ppm Adjusted BMC_{05} = 3.38 ppm BMC_{05} = 2.93 ppm excluding 400 ppm group	95% LCL_{05} = 15.3 ppm Adjusted 95% LCL_{05} = 0.95 ppm 95% LCL_{05} = 1.48 ppm excluding 400 ppm group	Chi-square (2) = 0.77 p-value = 0.00 (Chi-square (0) = 0.00 p-value = 1.00)
		control (n = 61) 25 ppm (n = 63) 100 ppm (n = 61) 400 ppm (n = 63)	females, centrilobular hepatocellular hypertrophy: 0 6% 19% (p < 0.05) 54% (p < 0.05)	BMC_{05} = 25.1 ppm Adjusted BMC_{05} = 4.48 ppm	95% LCL_{05} = 19.9 ppm Adjusted 95% LCL_{05} = 3.55 ppm	Chi-square (2) = 0.39 p-value = 0.82

TABLE 3 (continued)

Study (reference)	Effect level	Data for calculating benchmark concentration		Benchmark concentration[1]		
		Concentration	Response	Parameter estimates		Goodness of fit
		control (n = 31) 25 ppm (n = 42) 100 ppm (n = 38) 400 ppm (n = 36)	males, relative liver weight: 5.85 5.94 7.06 ($p < 0.05$) 7.80 ($p < 0.05$)	BMC_{05} = 65.6 ppm	95% LCL_{05} = 37.5 ppm	F(1,143) = 1.94 p-value = 0.17
				Adjusted BMC_{05} = 11.7 ppm	Adjusted 95% LCL_{05} = 6.69 ppm	
		control (n = 42) 25 ppm (n = 35) 100 ppm (n = 36) 400 ppm (n = 47)	females, relative liver weight: 5.59 5.71 5.99 6.35 ($p < 0.05$)	BMC_{05} = 144.7 ppm	95% LCL_{05} = 76.3 ppm	F(1,156) = 0.34 p-value = 0.56
				Adjusted BMC_{05} = 25.8 ppm	Adjusted 95% LCL_{05} = 13.6 ppm	

[1] Adjusted from intermittent exposure (hours/day, days/week) to continuous exposure.

TABLE 4 Effect levels and benchmark doses for DMF, oral exposure

Study (reference)	Effect level	Data for calculating benchmark dose		Benchmark dose		
		Concentration	Response	Parameter estimates		Goodness of fit
Subchronic assays						
Rat, Wistar 25 males and 25 females per group Dietary administration for 15 weeks (Becci *et al.*, 1983)	LOEL = 69 mg/kg-bw per day, based upon a significant increase in relative liver weight in females at the two highest doses (NOEL = 20 mg/kg-bw per day)	control (n = 25) 18 mg/kg-bw per day (n = 23) 61 mg/kg-bw per day (n = 25) 210 mg/kg-bw per day (n = 23)	males, relative liver weight: 4.30 ± 0.09 4.51 ± 0.11 4.59 ± 0.08 4.99 ± 0.10 ($p < 0.05$)	BMD_{05} = 23.1 mg/kg-bw per day	95% LCL_{05} = 12.7 mg/kg-bw per day	F(1,92) = 0.73 p-value = 0.39
		control (n = 25) 20 mg/kg-bw per day (n = 25) 69 mg/kg-bw per day (n = 24) 235 mg/kg-bw per day (n = 24)	females, relative liver weight: 3.86 ± 0.06 3.89 ± 0.08 4.24 ± 0.12 ($p < 0.05$) 5.00 ± 0.12 ($p < 0.05$)	BMD_{05} = 35.9 mg/kg-bw per day	95% LCL_{05} = 15.7 mg/kg-bw per day	F(1,94) = 0.13 p-value = 0.72
Mouse, CD-1 30 males and 30 females per group dietary administration for 17 weeks (Becci *et al.*, 1983)	LOEL = 96 mg/kg-bw per day, based upon statistically significant increase in relative liver weight in females NOEL = 28 mg/kg-bw per day	control (n = 30) 22 mg/kg-bw per day (n = 28) 70 mg/kg-bw per day (n = 29) 246 mg/kg-bw per day (n = 29)	males, relative liver weight: 5.3 ± 0.1 5.6 ± 0.1 5.8 ± 0.1 6.6 ± 0.1 ($p < 0.01$)	BMD_{05} = 21.3 mg/kg-bw per day	95% LCL_{05} = 7.6 mg/kg-bw per day	F(1,112) = 1.17 p-value = 0.28
		control (n = 30) 28 mg/kg-bw per day (n = 29) 96 mg/kg-bw per day (n = 29) 326 mg/kg-bw per day (n = 30)	females, relative liver weight: 5.1 ± 0.2 5.5 ± 0.1 5.9 ± 0.1 ($p < 0.01$) 6.6 ± 0.3 ($p < 0.01$)	BMD_{05} = 36.8 mg/kg-bw per day	95% LCL_{05} = 21.3 mg/kg-bw per day	F(1,114) = 0.14 p-value = 0.71

$$P(d) = q_0 + (1 - q_0) \cdot \left[1 - e^{-q_1 d - K - q_k d^k} \right]$$

where d is dose, k is the number of dose groups in the study, $P(d)$ is the probability of the animal developing the effect at dose d and $q_i > 0$, $i = 1,...,k$ are parameters to be estimated.

The models were fit to the incidence data using THRESH (Howe, 1995), and the BMC_{05}s were calculated as the concentration C that satisfies

$$\frac{P(C) - P(0)}{1 - P(0)} = 0.05$$

A chi-square lack of fit test was performed for each of the model fits. The degrees of freedom for this test are equal to k minus the number of q_i's whose estimates are non-zero. A p-value less than 0.05 indicates a significant lack of fit.

For the continuous endpoints, the BMC_{05} is defined as the concentration that causes a 5% increase in the absolute (i.e., additional) risk of seeing an "adverse" response. This method utilizes the "hybrid" method of Crump (1995), in which the adverse response level in the control group is specified as 5%. That is, 5% of the animals in the control group would, by natural variation, have a response that would be considered adverse. Then, the probability of being adverse, as opposed to the response itself, is modelled.

The Weibull model was fit to each of the endpoints using BENCH_C (Crump and Van Landingham, 1996):

$$P(d) = p_0 + (1 - p_0)\left[1 - e^{-(\beta d)^k}\right]$$

where d is dose, $P(d)$ is the probability of an adverse response at dose d and k, b, and p_0 are parameters to be estimated. The BMC_{05} was then calculated as the concentration C such that

$$P(C) - P(0) = 0.05$$

An F-test was used to assess lack of fit of the model. A p-value less than 0.05 indicates lack of fit.

Although not the basis of the TC developed here, there are several important observations from dose–response analyses of the results of the studies in animals. The lowest reported benchmarks for a range of hepatic effects in rats and mice following inhalation are those for histopathological lesions in the liver, which are higher but in the same range as those reported to induce effects on hepatic function in the studies in workers. It should be noted, though, that, due to the nature of the effects on which they were based (increases in serum hepatic enzymes versus histological effects), the benchmarks in humans and animals are not strictly comparable.

It is also evident that there is progression of effects from subchronic to long-term studies, with effects being more severe following chronic exposure (although quantitative values for the lowest benchmarks for different types of lesions in the subchronic and chronic studies are similar).

3.3.4 Human health risk characterization

Due to the nature of use, patterns of release and environmental fate of DMF, the focus of the human health risk characterization is populations exposed through air in the vicinity of industrial point sources (Section 3.3.1).

Worst-case estimates of airborne levels in the immediate vicinity of the largest emitter in Canada (0.11 mg/m^3), which are likely 10- to 100-fold greater than those anticipated under most conditions (Section 3.1.2.1), do not appreciably exceed the TC (0.1 mg/m^3) derived on the basis of increases in serum hepatic enzymes in exposed workers.

3.3.5 *Uncertainties and degree of confidence in human health risk characterization*

For the reasons mentioned in Sections 3.1.2.1 and 3.1.2.2, quantitative estimates of ambient levels in the vicinity of point sources in Canada on which the human health risk characterization is based are highly uncertain and likely conservative, although consistent with highest concentrations measured in other countries. The proximity of these predicted concentrations in the vicinity of point sources to residential areas is also unknown. Available monitoring data are inadequate as a basis for characterization of the exposure of the general population to DMF.

There is a high degree of confidence based on studies in both humans and experimental animals that the liver is the target organ for the toxicity of DMF. Cross-sectional studies on hepatic effects in workers, limited principally to males, were complicated by co-exposures to other substances and limitations of available data on exposure, including, in some cases, lack of monitoring data for individuals. However, the levels that induced minimally adverse hepatic effects were remarkably consistent across a large number of studies.

3.4 Conclusions

CEPA 1999 64(a): Based on available data, it is concluded that N,N-dimethylformamide is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity. Therefore, N,N-dimethylformamide is not considered to be "toxic" as defined under Paragraph 64(a) of CEPA 1999.

CEPA 1999 64(b): Based on available data, it is concluded that N,N-dimethylformamide is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends. Therefore, N,N-dimethylformamide is not considered to be "toxic" as defined under Paragraph 64(b) of CEPA 1999.

CEPA 1999 64(c): Based on available data, it has been concluded that N,N-dimethylformamide is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health. Therefore, N,N-dimethylformamide is not considered to be "toxic" as defined under Paragraph 64(c) of CEPA 1999.

Overall conclusion: Based on critical assessment of relevant information, N,N-dimethylformamide is not considered to be "toxic" as defined in Section 64 of CEPA 1999.

3.5 Considerations for follow-up (further action)

Since N,N-dimethylformamide is not considered "toxic" as defined in Section 64 of CEPA 1999, investigation of options to reduce exposure under CEPA 1999 is not considered a priority at this time. However, this is based upon current use patterns; thus, future releases of this compound should continue to be monitored to ensure that exposure does not increase to any significant extent.

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APPENDIX A SEARCH STRATEGIES EMPLOYED FOR IDENTIFICATION OF RELEVANT DATA

Environmental assessment

Data relevant to the assessment of whether DMF is "toxic" to the environment under CEPA were identified from existing review documents, published reference texts and on-line searches conducted between January and May 1996 of the following databases: Aqualine (1990–1996), ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1996), BIOSIS (Biosciences Information Services; 1990–1996), CAB (Commonwealth Agriculture Bureaux; 1990–1996), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources; 1996), Chemical Abstracts (Chemical Abstracts Service, Columbus, Ohio; 1990–1996), CHRIS (Chemical Hazard Release Information System; 1964–1985), Current Contents (Institute for Scientific Information; 1990–1992, 1996), ELIAS (Environmental Library Integrated Automated System, Environment Canada library; January 1996), Enviroline (R.R. Bowker Publishing Co.; November 1995 – June 1996), Environmental Abstracts (1975 – February 1996), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara; 1990–1996), GEOREF (Geo Reference Information System, American Geological Institute; 1990–1996), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine; 1990–1996), Life Sciences (Cambridge Scientific Abstracts; 1990–1996), NTIS (National Technical Information Service, U.S. Department of Commerce; 1990–1996), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1996), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1995), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health; 1996), Toxline (U.S. National Library of Medicine; 1990–1996), TRI93 (Toxic Chemical Release Inventory, U.S. Environmental Protection Agency, Office of Toxic Substances; 1993), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, U.S. Environmental Protection Agency; up to December 21, 1994), WASTEINFO (Waste Management Information Bureau of the American Energy Agency; 1973 – September 1995) and Water Resources Abstracts (U.S. Geological Survey, U.S. Department of the Interior; 1990–1996). A survey of Canadian industry was carried out under authority of Section 16 of CEPA (Environment Canada, 1997c). Companies were required to provide information on uses, releases, environmental concentrations, effects or other data that were available to them for DMF. Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the potential environmental effects of DMF. Data obtained after September 1999 were not considered in this assessment unless they were critical data received during the 60-day public review of the report (June 3 to August 2, 2000).

Health assessment

To identify data relevant to the estimation of exposure of the general human population to DMF, on-line literature searches were conducted (in February 1994) on the following databases: AQUAREF (Inland Waters Directorate, Environment Canada), EMBASE (on-line version of Excerpta Medica) and Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine). Subsequently, a selective dissemination of information (SDI) profile was

used to identify new literature on an ongoing basis. In addition, numerous provincial officials and representatives of various industrial sectors were contacted for monitoring data relevant to exposure and effects. Data relevant to the assessment of human health were identified and summarized by BIBRA International (1999). Data obtained after February 2000 were not considered in this assessment.